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# RESEARCH & DEVELOPMENT

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# *content*

# *Morphological and Immunohistochemical Features of Diffuse Idiopathic Pulmonary Neuroendocrine Cell Hyperplasia: Aguayo - Miller Disease*

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**Abstract**

*Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) is a rare pulmonary disorder that is characterized hyperplasia of bronchiolar and bronchial pulmonary neuroendocrine cells. The hyperplasia of neuroendocrine cells can be primary or reactive. In the WHO - IASLP classification of lung tumours (1999, 2004, 2005, 2015), DIPNECH is considered a preneoplastic lesion in the spectrum of pulmonary tumours. According to the WHO classification, the definition of DIPNECH is purely histological. The histological appearance of DIPNECH within the lungs takes many forms. It may comprise a diffuse hyperplasia of scattered neuroendocrine cells, small nodules (neuroendocrine bodies), or a linear proliferation in alveolar ducts and alveols. These proliferations are superficial to the basement membrane and confined to the bronchial and bronchiolar epithelium. When there is extension beyond the basement membrane, the neuroendocrine cell proliferations in the multiple nodules < 5 mm diameter are termed tumourlets, but where the tumourlets have > 5 mm diameter are classified carcinoid tumours.*

*The DIPNECH was initially described in 1992 by Aguayo et al., who reported six non-smoking patients with cough, exertional dyspnea, wheezing, less frequently*

*hemoptysis and a mixed obstructive/restrictive defect on pulmonary function tests. In the Aguayo – Miller disease, the DIPNECH is a primary proliferation and is associated with tumourlets and carcinoid and with obstructive bronchiolitis. This disease has a predilection for nonsmoking middle-aged women (female to male ratio it's approximately 10:1)*

*In this study we present a 62-year-old, non-smoker woman, presented with respiratory symptoms ascribable to DIPNECH. After surgery, the morphological study of lung specimens, conferme the DIPNECH, multiple tumourlets, one peripheral carcinoid and obliterative bronchiolitis in the right middle pulmonary lobe.*

***Key words:*** *Neuroendocrine pulmonary cell hyperplasia, tumourlets, carcinoid, obliterative* bronchiolitis.

## Introduction

Neuroendocrine cells are component of the normal bronchiolar and bronchial epithelium, that comprise about 1 % of epithelial cells in an adult lung. These cells expressed neuroendocrine markers (chromogranin A, synaptophysin, CD 56 etc.) DIPNECH is a clinico-pathological syndrome, as well as an incidental finding on histological examination, althought there are obvious differences between these two scenarios. [1 - 5] When no other pathological pulmonary disease is detected, DIPNECH is idiopathic, instead the reactive neuroendocrine hyperplasia is believed to be a response to hypoxia and chronic obstructive pulmonary disease as interstitial fibrosis, asthma, cystic fibrosis, bronchopulmonary dysplasia, bronchiectasis, chronic obstructive pulmonary disease, and also in the neuroendocrine pulmonary tumours, non endocrine pulmonary tumours, chronic exposure to high altitude, exposure to tobacco smoke etc. [2, 3, 4, 5, 6.] In WHO classification of tumours of the lung (1999, 2004, 2005, 2015), the DIPNECH was defined a preneoplastic lesion, because it is commonly found in patients with tumourlets and carcinoid tumours. [2, 3, 4, 5] According to the WHO classification, the definition of DIPNECH is purely histological. However, DIPNECH encompasses asymptomatic patients with airway disease, as well as symptomatic patients with pulmonary neuroedocrine cell hyperplasia associated with multiple tumourlets and carcinoid tumors. [1, 2, 3, 4, 5]

Histologically, the DIPNECH may manifest as: a. generalised proliferation of scattered neuroendocrine cells; b. tinely nodular aggregates (neuroendocrine body); c. linear proliferation. Althought usually confined to the bronchial and bronchiolar epithelium, these proliferation can extend beyond the basement membrane to form tumourlts, or carcinoid tumours, lesions which have continuity and correlation. [1, 6, 7, 8, 9]

The disease Aguayo – Miller is characterized by diffuse idiopathic hyperplasia of scattered neuroendocrine cells in the distal bronchi and bronchioles, a linear hyperplasia in alveolar ducts and alveols, associated with multiple tumourlets and peripheric carcinoid and peribronchiolar fibrosis obliterating small airways, and by mild chronic lymphocytic inflammation. [1, 3, 4, 5, 6, 7]

This disease was initially described in 1992 by Aguayo et al., who reported six non-smoking patients with cough, exertional dyspnea, wheezing, less frequently hemoptysis and a mixed obstructive/restrictive defect on pulmonary function tests. [1, 2, 6, 8, 9]

There have now been more than 200 cases of this disease, published since the initial description by Aguayo in 1992, in the form of case reports or small case series, but no clear consensus has been established in the literature about the radiological or pathological diagnostic criteria, or the management of this disease. [3, 6, 10]

## Case report

A 62-year-old woman, non-smoking, presented with a respiratory tract infection, expressed with cough, exertional dyspnea, and wheezing. The radiography and the high-resolution computed tomography (HRCT) of the chest, showed a mosaic attenuation do to interstitial fibrosis, and presence of some little nodules and a nodule measuring 28 mm, in the right middle pulmonary lobe.

The lung function tests show an obstructive ventilation defect. After the lobe resection, the microscopic examination (histopathology and immunohistochemistry), confirme the diagnosis of diffuse idiopathic pulmonary neuroendocrine cells hyperplasia, multiple tumourlets, one carcinoid tumours and obliterative bronchiolitis with peribronchiolar fibrosis obliterating small airways, and intertstitial chronic inflammation. The patient was followed according to standard follow-up for patients after lobe resection. She is alive and well 4 year after surgery.

## Pathologic findings

In the histopathologically examination (haematoxyline & eosine staining) of lung surgical specimens, we have revealed diffuse idiopathic hyperplasia of pulmonary neuroendocrine cells involved distal bronchi and bronchioles with numerous neuroepithelial bodies present within the mucosa. (Figure 1). The neurondocrine cells are round, or oval shape, monomorphe size, with less citoplasme, large nuclei deeple stained, or are fine granular-like, nucleoli are unobvious. Neuroendocrine

cells are scattered in individual ones or at line-like, or form small nests in the bronchiolar epithelium, and even completely replace bronchiolar epiethelium, resulting in narrow lumen but not penetring basament membrane. These neuroendocrine cells hyperplasia is complicated with obliterative bronchiolitis. The residual airway lumen is replaced by nodular and circumfe-rential arrangement of neuroendocrine cells, expressed with peribronchiolar fibrosis obliterating small airways, and associated wit a little interstitial chronic inflamation. (Figure 2) In some fields we have seen the lineare neuroendocrine cells hyperplasia in alveolar ducts and alveoli (Figure 1). No mitotic figures, no areas of necrosis, no cell pleomorphism were detected in the proliferative neuroendocrine cells.

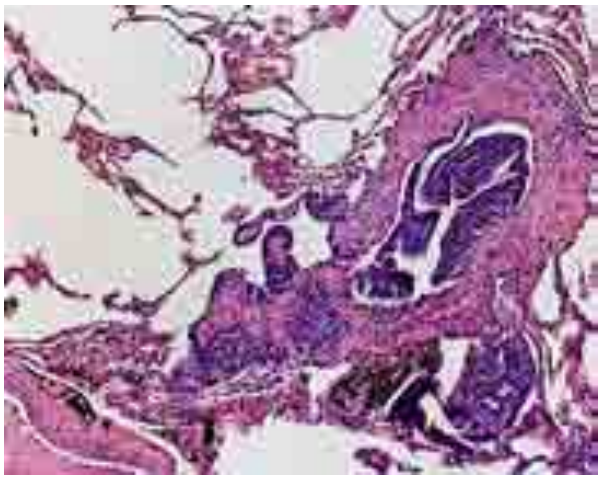

**FIGURE 1.** Neuroendocrine cells involved bronchioles with numerous neuroepithelial bodies present within the mucosa, and two tumourlets.

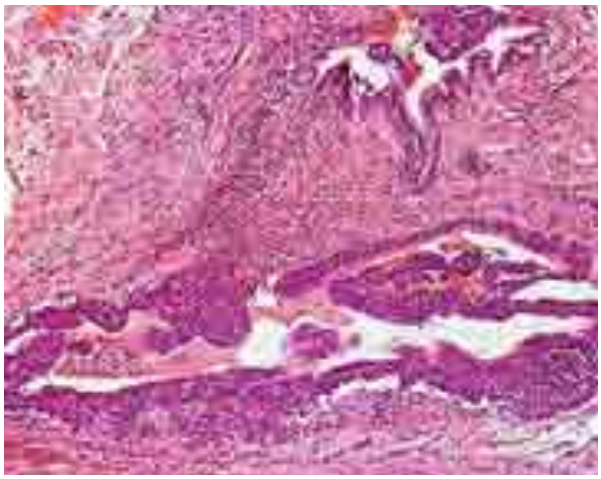

**FIGURE 2.** The residual airway lumen is replaced by nodular and circumferential arrangement of NEP cells, associated peribronchiolar fibrosis and interstitial chronic inflamation.

**FIGURE 3.** Immunohistochemical staining. Neuroendocrine pulmonary cells positive for chromogranin A.

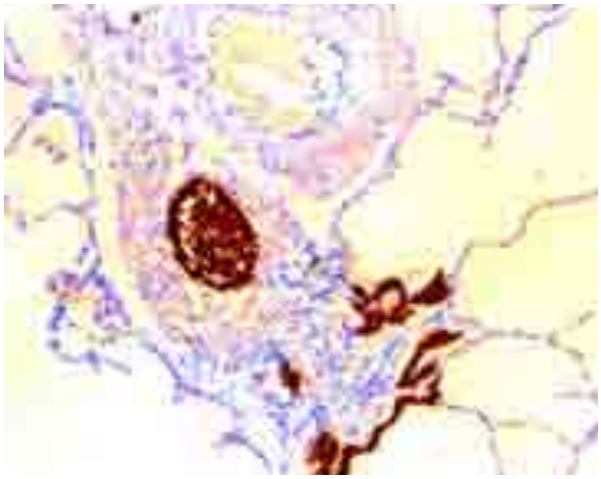

**FIGURE 4.** Linear proliferation of NEP cells in the alveolar ducts and alveoli, positive for chromogranin A

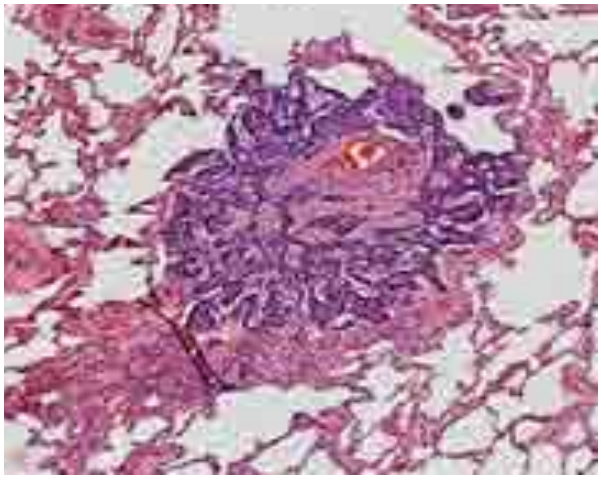

**FIGURE 5.** Tumourlet: neuroendocrine cells are embedded an dense fibroelastic stroma

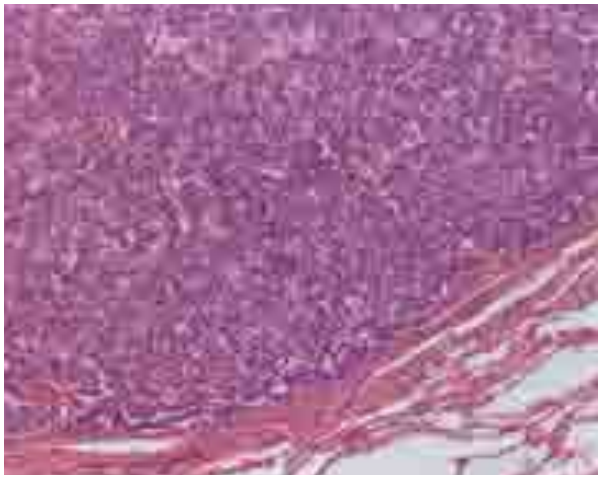

**FIGURE 6.** Typical carcinoid is circumscribed but not encapsulated.

In the immunohistochemical staining we have revealed the neuroendocrine cells involving distal bronchi and bronchioles (Fig 3) and linear proliferation in the alveolar ducts and alveoli contains neurosecretory granules wich are positive for chromogranin A (Fig. 4), and for synaptophysine, and for CD56, which is a marker of neuroendocrine cell differentiation. At least nine tumorlets, were found in the peribronchial region of the right middle pulmonary lobe, of varying size and morphologic features. The tumourlets are 2 – 4 mm sized nodular hyperplasia of neuroendocrine cells, that are embedded in dense fibroelastic connective tissue. (Figure 5). Movat's pentachrome staining demonstrated a abnormal deposition of disorganized collagen and elastic fibers in both the tumorlets and the submucosa underlying areas of pulmonary neuroendocrine cells hyperplasia in small airways not obliterated by tumorlets.

In the immunohistochemical stains, the neuroendocrine cells of tumourlets presents positivity for chromogranin A (Figure 3 and Figure 4), synaptophysine, Neuron Specific Enolase, CD56, and bombesine. The proliferative activity with Ki67 < 1 % in the tumourlets.

We have detected a typical carcinoid with 28 mm diameter in the parenchima of the right middle pulmonary lobe. The typical carcinoid is circumscribed, but not encapsulated, and have nests of uniform cells, covered in the elegant fibrovascular stroma. (Figure 6). The cytologic apparence of neuroendocrine cells of carcinoid is basically the same: monomorphic cells population with scarce eosinophilic cytoplasm, monomorphic central nucleus with finely granular chromatin as "salt and pepper". The neuroendocrine cells were arranged delimiting nests, without necrosis and with 1 - 2 mitosis in 10 hpf, but without significant atypia.

In the immunohistochemical staining, the neuroendocrine cells of typical carcinoid was positive for chromogranin A, synaptophysine, Neuron Specific Enolase, CD56, also have EGF focal expression, VEGF modest expression, and Bax over expression. Proliferative activity with Ki-67 < 3 %.

## Discussion

Pulmonary Neuroendocrine cells are part of normal epithelium of bronchial and bronchiolar anatomy and are thought to play an important role in lung development, as they are frequently found in the airways of fetal and neonatal lungs [1, 3]. Neuroendocrine cells of the lung decrease in number with age and are only present focally in adult airways, where they represent approximately 1% of all epithelial cells in the adult lung [2, 3] Pulmonary neuroendocrine cell hyperplasia can be either primary or reactive. It is important to emphasize, that the DIPNECH is defined as being idiopathic, so existing without any pre-existing chronic lung disease and in the absence of other lung diseases, but reactive pulmonary neuroendocrine cells hyperplasia can occur as a result of a wide spectrum of chronic conditions that are expressed with hypoxia, including pulmonary interstitial fibrosis, asthma, cystic fibrosis, bronchopulmonary dysplasia, bronchiectasis, chronic obstructive pulmonary disease, neuroendocrine lung tumours, non neuroendocrine lung tumours, chronic exposure to high altitude, exposure to tobacco smoke etc. [2, 3, 4, 5, 6, 7.].

The first series of six cases of DIPNECH was published by Aguayo et al., in 1992 [1], describing a clinical condition with respiratory symptoms as well as specific radiological and histological characteristics. The treatments of these patients included the lobe or the lung resection. [1, 2, 3, 5, 8, 9].

The WHO classification 2015 has considered the DIPNECH a precancerous lesion of a lung neuroendocrine tumour, it is defined as within broncchial mucosal epithelium, there is duffuse clustered, linear or nodular neuroencdocrine ccell hyperplasia without basement membrane breaakthrough. [2, 3, 4, 6, 10, 11, 12]. The current definition of DIPNECH by the WHO is exclusively histological. [3, 6, 11, 12, 13, 14]. There have now been more than 200 cases of DIPNECH described since the initial description by Aguayo, in the form of case reports or small case series, but no clear consensus has been established in the literature about the radiological or pathological diagnostic criteria or the management of this condition. [6, 10, 11, 12]. DIPNECH has a predilection for nonsmoking, middle-aged women and is associated with a predominantly obstructive ventilatory pattern on pulmonary function tests seen in obliterative bronchiolar fibrosis. [1, 3, 5, 6, 14]

The diagnosis of DIPNECH is often made several years after the onset of clinical

symptoms, usually following the incidental discovery of a lung nodule on chest radiography or CT scan. The condition progresses slowly, although there have been cases reported of a rapidly progressive and more aggressive clinical course, which has required lobectomy or pulmonectomy, and even lung transplantation. [6, 10, 11, 12, 14].

There seems to be two different modes of clinical presentation of DIPNECH. Onset is occult, there may be no clinical symptoms, or there is long duration of dry cough, and exertional dyspnea, expressed with obstructive – restrictive lung function profile, but these cases clinically are commonly misdiagnosed for bronchial asthma or chronic bronchitis. [5, 6, 9, 12, 13]. DIPNECH is often accompanied with chronic airway inflammation and diseases that can cause severe interstitial pulmonary fibrosis. [4, 6, 10, 11, 12, 15, 16].

Our case have similar clinico-morphological characteristics to symptomatic forme to those published.

Under a light microscope, our case present hyperplasia of pulmonary neuroendocrine cells, confined within bronchial mucosal epithelium and manifest as round, or oval cells, with relatively consistent size and shape showing: hyperplasia, less cytoplasm, large nuclei deeply stained, or are chromatine fine granule-like, nucleoli are unobvious. Neuroendocrine cells are scattered in individual ones, or form small nests at base of bronchiolar epithelium, and even completely replace bronchiolar epithelium, resulting in narrow lumen, but not penetrating basement membrane. These neuroendocrine cells hyperplasia is complicated with obliterative bronchiolitis. In some fields we have seen the lineare neuroendocrine cells hyperplasia in alveolar ducts and alveoli (Figure 1 and Figure 4). The residual airway lumen is replaced by nodular and circumferential arrangement of neuroendocrine cells, expressed with peribronchiolar fibrosis obliterating small airways, and associated with interstitial fibrosis and chronic inflamation. (Figure 2). No atypical mitotic figures, no areas of necrosis, no cell pleomorphism were detected in the proliferative neuroendocrine cells.

In some other fields we have seen the neuroendocrine cells penetrate basement membrane to infiltrate lung interstitium and show nodular growth, which are tumourlets.

In the immunohistochemical staining we have revealed the neuroendocrine cells involving distal bronchi and bronchioles (Figure 3) and linear proliferation in the alveolar ducts and alveoli contains neurosecretory granules wich are positive for chromogranin A (Figure 4), and for synaptophysine, and for CD56, which is a marker of neuroendocrine cell differentiation.

We have identificate nine tumorlets, which were found in the peribronchial region. The tumourlets 2 – 4 mm sized, present nodular hyperplasia of neuroendocrine cells, that are embedded in dense fibroelastic connective tissue.

(Figure 5) In the immunohistochemical stains, the neuroendocrine cells presents positivity for chromogranin A (Figure 3), synaptophysine, Neuron Specific Enolase, CD56, and for bombesine. The nodular proliferation of neuroendocrine cells, formed lesions with a diameter < 5 mm are considered to be tumourlets, but where the nodules are > 5 mm, are classified as typical carcinoid tumour. [3, 5, 6, 7, 8, 9]. Also, we have diagnosed a typical carcinoid tumour (28 mm diameter) in the right middle pulmonary lobe.

In the immunohistochemical study, the neuroendocrine cells of carcinoid are positive for chromogranin A, synaptophysine, Neuron Specific Enolase, CD56, also have EGF focal expression, VEGF modest expression, and Bax over expression. Proliferative activity with Ki-67 < 3 %.

DIPNECH is regarded as a precursor lesion for tumourlets and carcinoid tumors. [3, 6, 10, 14, 15, 16]

The carcinoid is subdivided into: typical carcinoid, which is low grade tumour and atypical carcinoid, which is intermediate grade tumour. [3, 4, 6] In the series by Davies et al.[13], there were three cases associated with atypical carcinoid, one of whom had multiple endocrine neoplasia. This is the first case with a classic clinical picture of DIPNECH with metastatic carcinoid and multiple unrelated tumors. [6, 13]

The morphological diagnosis of our case is: Aguayo – Miller disease: DIPNECCH in the distal bronchial and bronchiolar wall, the linear proliferation confined to the alveolar duct and alveola, presence of multiple tumourlets, one carcinoid tumour and obliterative bronchiolitis, interstitial fibrosis associated with chronic interstitial inflammation.

However, a recent paper by Marchevsky et al. [11] reported on 70 consecutive surgical lung biopsies showing multifocal neuroendocrine proliferations, which had neither histological features of obliterative bronchiolitis nor had they been diagnosed with DIPNECH before histological examination, indicating that the condition can be asymptomatic [13]. This study suggested that the presence of multifocal PNECH combined with more than three tumorlets as the minimum pathological criteria for the diagnosis of DIPNECH, limiting the condition to a pathological entity. [7] A pathology-based approach by Marchevsky aimed at distinguishing DIPNECH from reactive neuroendocrine cell hyperplasia, suggested that the presence of multifocal NECH associated with more three tumorlets could represent a pathological criterion for the diagnosis of DIPNECH.

Wirtschafter and al. [12] evaluated 30 cases of DIPNECH and systematically reviewed 169 cases reported in the English literature and concluded that only 55 (28 %) had obliterative or constrictive bronchiolitis. This same conclusion has been drawn by Davies and al [11, 13], who suggest that even in cases with histological evidence of airway wall thickening, chronic inflammation, and constrictive obliterative bronchiolitis, the majority of patients did not have clinically important

airflow obstruction. [8, 10, 11, 12, 13] With regard to symptomatic cases of DIPNECH, as in the case we have presented, the condition typically presents with a chronic cough, exertional dyspnea, and frequent wheezing, with a clinical presentation predominantly in non-smoking middle-aged women. In the appropriate clinical and radiological setting, a transbronchial biopsy may be sufficient for diagnosis of DIPNECH, although open surgical lung biopsy is considered optimum for diagnosis [3, 9, 10, 12, 13, 14, 16].

The histological features of DIPNECH include constrictive/obliterative bronchiolitis characterized by chronic inflammation, bronchial wall thickening and fibrosis, believed to be the reason for progressive narrowing and/or complete obliteration of the bronchiolar lumen in severe cases. [3, 12, 13, 14, 16, 17, 18, 19 , 20].

The chromogranin A, synaptophysin, and CD56 are the most commonly expressed immunohisto-chemical markers, while p53, Ki-67, and p16 may distinguish DIPNECH from reactive pulmonary NECH. [3].

The patient profile and presentation in this case report fits the typical DIPNECH profile, that of a middle-aged non-smoking female presenting with exertional dyspnea, in association with the discovery of a lung nodule on chest CT [3, 8]. The biopsy findings are those of the histological criteria for DIPNECH diagnosis as defined by the WHO and cited by Marchevsky et al. [3, 7, 9, 11]

The treatment for our case was surgery (lobectomy), but some authors use the somatostatin analogs (SSA) in DIPNECH. [17, 18] Gorshtein et al., in their review of 11 DIPNECH patients, suggested the affirmative role of SSA in the symptom management of DIPNECH. In the American single-center experience, most of their patients responded to treatment with SSA and had significant improvement in their presenting symptoms. [18]

## Conclusions

DIPNECH remains a rare pulmonary condition, and considered a preneoplastic lesion in the spectrum of pulmonary tumours. According to the WHO classification, the definition of DIPNECH is purely histological. While most patients experience a relatively uneventful clinical course, this condition may be associated with tumourlets, carcinoid tumour and airway obstruction (Aguayo-Miller disease). Awareness of the condition, imaging, and histopathology are required to make the definitive diagnosis, and close follow-up is important in the more aggressive cases of DIPNECH.

It is possible that DIPNECH is an under-diagnosed pulmonary condition because it is rarely associated with symptoms. This case report has highlighted this rare, but potentially progressive condition and the need for evidence-based management guidelines for DIPNECH.

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# *Hypertensive Disease in Pregnancy - A Retrospective Study*

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## Abstract

***Introduction***: *Hypertensive disease in pregnancy is a group of high blood pressure disorders that occur during pregnancy and is classified into 4 categories: pregnancy-induced hypertension (PIH), chronic hypertension, preeclampsia-eclampsia and preeclampsia superimposed on chronic hypertension. About 10% of pregnancies globally are complicated by hypertensive diseases. Hypertensive disease in pregnancy,*

*are one of the three major causes of death in pregnancy (16%) along with postpartum bleeding (13%) and puerperal infections (2%*

***Aim:*** *The purpose of this study was to determine the frequency of hypertensive disease in pregnancy and the perinatal outcomes of women with hypertensive disease in pregnancy.*

***Method****: This was a retrospective study of hypertensive disease in pregnancy at the Obstetrics and Gynecology Clinic / University Clinical Centre in Kosovo. The data was obtained from the hospitalized patient's medical history. Sample size: 8754 cases. Data collection, classification, and statistical analysis were performed with SPSS 21.*

***Results:****Out of 8754 observed pregnant women, 84 or 10.4% of them had the hypertensive disease in pregnancy; of them, 59.5% (50) had pregnancy-induced hypertension (PIH), 20.2%(17) preeclampsia, 14.3% (12) chronic hypertension, and 6% (5) eclampsia. The average age of women with the hypertensive disease in pregnancy was 26.6 +- 2; where 27.5% (23) of them were women over 35 years of age, while 3.5% of them were under 18 years of age. Out of 84 women; 53.5% (45) were multiparous women, while 46.5% (39) were primiparous women. 41.7% (35) of women with hypertensive pregnancy disease are born with a Cesarean section, while 58.3% (49) are born with vaginal delivery. 79.7% of infants were born with an Apgar score of over 5, 13% below 5, while 7.3% were morsfoetus.*

***Conclusions:*** *The prevalence of hypertension in pregnancy at the Obstetrics and Gynecology Clinic in Pristina was 10.4%. 27.5% of women with the hypertensive disease in pregnancy were women over 35 years of age, while 3.5% of them were under 18 years of age. Hypertensive disease in pregnancy occurs more frequently in multiparous women. Due to emergencies, almost half of women with hypertensive pregnancy disease are born with a Cesarean section, and 80% of infants are born with an Apgar score of over 5.*

***Key words:*** *Hypertensive disease in pregnancy; Prevalence; Kosovo*

## Introduction

While motherhood is a positive and enjoyable experience, many women are experiencing somewhat of a health disturbance on their pregnancy months, either that is a sort of an acute illness or a prolong disease.[1]

Around 15% of pregnant women are expected to develop life-threatening complications during pregnancy, at delivery or post-partum.

Hypertension is the most common medical problem encountered during pregnancy, complicating 2-3% of pregnancies.Hypertensive disorders during pregnancy are classified into 4 categories, as recommended by the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy: chronic

hypertension, preeclampsia-eclampsia, preeclampsia superimposed on chronic hypertension, and gestational hypertension (transient hypertension of pregnancy or chronic hypertension identified in the latter half of pregnancy) [2]

Chronic hypertension is high blood pressure that either precedes pregnancy, is usually diagnosed within the first 20 weeks of pregnancy, or does not resolve by the 12-week postpartum checkup. Two categories of severity are recognized: mild (up to 179 mm Hg systolic and 109 mm Hg) and severe (≥ 180 systolic or 110 diastolic). Chronic hypertension complicates about 5% of all pregnancies, and prevalence rates are increasing year by year because of delayed childbearing.[3]. Medications should be reviewed when pregnancy is first diagnosed or in the time when the couple is planning to get pregnant. Methyldopa is the most studied of all antihypertensive medications and is generally the first choice in pregnancy because it has a limited effect on uteroplacental blood flow [4].Sometimes an alternative must be found because of elevated liver enzymes or complaints of headache. Labetalol, a combined alphablocker and beta-blocker, is the first alternative to methyldopa and is becoming a first-line choice as experience with the drug during pregnancy increases. It is generally well tolerated and has an easier (twice-a-day) dosing schedule than methyldopa. [5].

Most studies have not found adverse pregnancy outcomes. Nonetheless, caution should be used in cases of impaired uteroplacental perfusion, such as preeclampsia or intrauterine growth restriction. Atenolol and other pure beta-blockers should be avoided: they have been associated with babies born small for their gestational age. Angiotensin-converting enzyme (ACE) inhibitors are contraindicated in the second and third trimester because they are associated with a myriad of congenital anomalies, including renal failure, oligohydramnios, renal dysgenesis, reduced ossification, pulmonary hypoplasia, and fetal and neonatal death. [6]

Complication rates are directly related to the severity and duration of elevated blood pressures. For instance, patients with severe hypertension in the first trimester have a greater than 50% risk of developing superimposed preeclampsia. [7] All hypertensive patients should undergo increased surveillance, serial laboratory tests throughout pregnancy, serial ultrasound scans to follow growth, and antenatal testing. The baby should be delivered normally that means in vaginal ways if possible.

Gestational hypertension, formerly known as pregnancy-induced hypertension or PIH, is the new onset of hypertension after 20 weeks of gestation.[12]

The diagnosis can be set as soon as the patient has:

- High blood pressure (systolic ≥ 140 or diastolic ≥ 90 mm Hg, the latter measured using the fifth Korotkoff sound)
- No protein in the urine
- Previously normal blood pressures
- No manifestations of preeclampsia.

Also known as transient hypertension, gestational hypertension is actually diagnosed retrospectively when the patient does not develop preeclampsia and if blood pressure returns to normal by the 12-week postpartum visit. Fifty percent of women diagnosed with gestational hypertension are between 24 and 35 weeks develop preeclampsia [8]

Preeclampsia is a multiorgan disease process of unknown etiology [9] characterized by the development of hypertension and proteinuria after 20 weeks of gestation.

Preeclampsia is defined as elevated blood pressure after 20 weeks of gestation (≥ 140 mm Hg systolic or ≥ 90 mm Hg diastolic) plus proteinuria (> 0.3 g/24 hours). In clinical practice, we usually use the criteria of two elevated bloodpressure measurements 6 hours apart and a proteinuria of 300 mg in a 24-hour urine specimen. A 24-hour determination is most accurate because urine dipsticks can be affected by variable excretion, maternal dehydration, and bacteriuria[10]

Preeclampsia can range from mild to severe. Severe preeclampsia is defined as any of the following:

- Markedly elevated blood pressure measurements (systolic ≥ 160 mm Hg or diastolic ≥ 110 mm Hg) taken at least 6 hours apart with the patient on bed rest
- Proteinuria (≥ 5 g/24 hours or ≥ 3+ on two random samples 4 hours apart)
- Manifestations of end-organ disease: oliguria (< 500 mL in 24 hours), cerebral or visual disturbances, pulmonary edema, cyanosis, epigastric or right-upperquadrant pain, impaired liver function, thrombocytopenia, or fetal growth restriction.

HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets) used to be classified as a separate syndrome, but current thinking categorizes it as a manifestation of preeclampsia, occurring in about 20% of severe cases. It is associated with significant maternal and perinatal morbidity. A decreasing platelet count and an increasing l-lactate dehydrogenase level (indicative of both hemolysis and liver dysfunction) reflect disease severity[11], [12]

Preeclampsia places both mother and fetus at risk. It is, however, a maternal disorder. The mainstay of treatment is early detection and managed delivery to minimize both maternal and fetal risks. Magnesium sulfate is still the drug of choice for preventing and arresting eclamptic seizures. It has the additional benefit of reducing the incidence of placental abruption [13]. Serum magnesium levels should be monitored in women with elevated serum creatinine levels, decreased urine output, or absent deep tendon reflexes [14]. Antihypertensive medications are used solely to prevent maternal morbidity and have no effect on disease progression or preventing eclampsia.

Medications must be given with caution: if blood pressure is lowered too fast, it can have a dramatic effect on uteroplacental perfusion and can cause an already compromised fetus to rapidly decompensate and become bradycardic. Preferred medications are hydralazine (5-10 mg intravenous bolus every 10-15 minutes), labetalol, nicardipine, and sodium nitroprusside. Intravenous labetalol and hydralazine are commonly used for the acute management of preeclampsia [15].

Although many pregnant women with high blood pressure have healthy babies without serious problems, high blood pressure can be dangerous for both the mother and the fetus therefore it should be detected and soon diagnosed so we can manage it and escape from such problems.

## Aim

The purpose of this study was to determine the frequency of hypertensive disease in pregnancy and the perinatal outcomes of women with hypertensive disease in pregnancy.

## Materials and methods

This was a retrospective study of hypertensive disease in pregnancy at the Obstetrics and Gynecology Clinic / University Clinical Centre in Kosova. The data was obtained from the hospitalized patient's medical history. Sample size: 8754 cases. Data collection, classification, and statistical analysis were performed with SPSS 21.This study was conducted during a year from 2017 to 2018

All pregnant women that were hospitalized in University Clinical Centre of Kosova were eligible to be included in this study.

Hypertensive disorders in pregnancy were diagnosed based on the diagnostic criteria set by the National High Blood Pressure Education Program Working Group.[8]

Pregnant women were in a randomized selection for the study. In this study to get better results different data was collected such as their previous pregnancies, way of delivery, their babies health condition also their age.

## Results

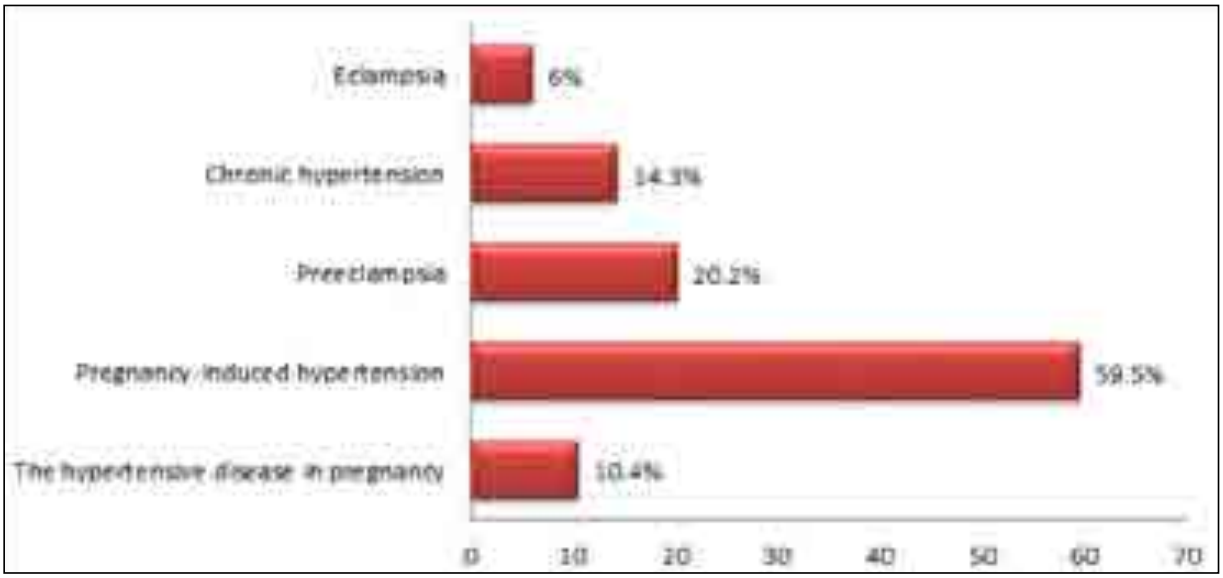
Out of 8754 observed pregnant women, 84 or 10.4% of them had the hypertensive disease in pregnancy; of them, 59.5% (50) had pregnancy-induced hypertension

(PIH), 20.2%(17) preeclampsia, 14.3% (12) chronic hypertension, and 6% (5) eclampsia.

**TABLE 1.** The most common hypertensive disorder in pregnant women

| | N | % |
|---|---|---|
| The hypertensive disease in pregnancy | 84 | 10.4 |
| Pregnancy-induced hypertension | 50 | 59.5 |
| Preeclampsia | 17 | 20.2 |
| Chronic hypertension | 12 | 14.3 |
| Eclampsia | 5 | 6 |
| TOTAL | 168 | 100 |

**CHART 1.** The most common hypertensive disorder in pregnant women expressed in percent



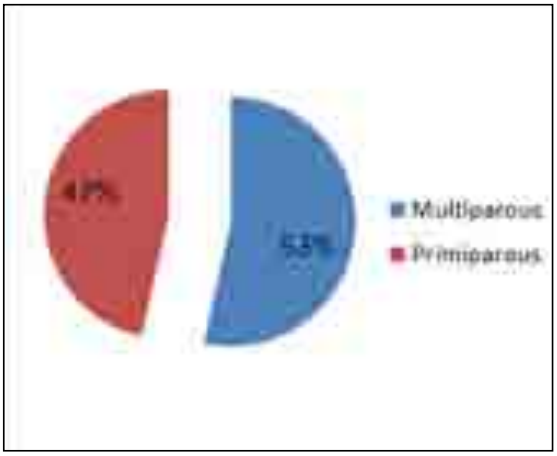

The average age of women with the hypertensive disease in pregnancy was 26.6 +- 2; where 27.5% (23) of them were women over 35 years of age, while 3.5% of them were under 18 years of age.

**TABLE 2.** The age groups of women that were studied

| AGE | % |
|---|---|
| <18 | 3.5 |
| 18-34 | 69 |
| >35 | 27.5 |

Out of 84 women; 53.5% (45) were multiparous women, while 46.5% (39) were primiparous women.

**CHART 2.S** eparated groups based on previous pregnancies of the pregnant women



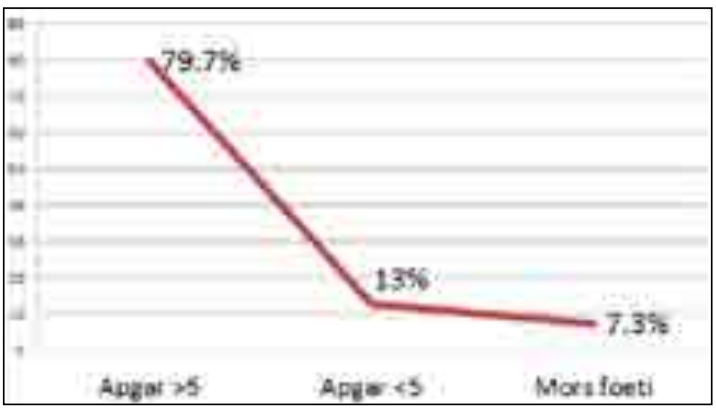

41.7% (35) of women with hypertensive pregnancy disease are born with a Cesarean section, while 58.3% (49) are born with vaginal delivery.

**TABLE 3.** The way of delivery of pregnant women with hypertensive disease in pregnancy

| Way of delivery | N | % |
|---|---|---|
| Cesarean Section | 35 | 41.7 |
| Vaginal Delivery | 49 | 58.3 |
| TOTAL women with hypertensive disease in pregnancy | 84 | 100 |

79.7% of infants were born with an Apgar score of over 5, 13% below 5, while 7.3% were morsfoeti Chart 3

**CHART 3.** Health conditions of the infants



## Conclusions

We concluded that the prevalence of hypertension in pregnancy at the Obstetrics and Gynecology Clinic in Pristina was 10.4%.

About the age 27.5% of women with the hypertensive disease in pregnancy were women over 35 years of age, while 3.5% of them were under 18 years of age. Our study provides that hypertensive disease in pregnancy occurs more frequently in multiparous women such it shows in our study. Due to emergencies, almost half of women with hypertensive pregnancy disease are born with a Cesarean section, and 80% of infants are born with an Apgar score of over 5.

## Discussion

This study determined adverse maternal and perinatal outcomes among women with Health Disease in Pregnancies and directly compared these adverse pregnancy outcomes between women with chronic/gestational hypertension and those with pre-eclampsia/eclampsia. The sociodemographic and reproductive characteristics did not differ significantly between the two groups except for prim paternity. Hypertensive disorders of pregnancy are the commonest medical complication of pregnancy. The incidence varies in different populations. Generally, the problem is more common in the developing countries compared to developed countries

According to the results of this meta-analysis, the pooled prevalence of hypertension disorder of pregnancy in Ethiopia was estimated to be 6.25% (95% CI: 5.23%, 7.26%). Regional variation in Health Disease In Pregnancy was observed, the highest prevalence of Health Disease In Pregnancy (18.25%) was reported in a study done in Public Health Institutions in Arba Minch town[16]

The overall pooled prevalence of hypertensive disorders of pregnancy in this study is more or less similar to the large study conducted on Health Disease In Pregnancy in China which was estimated 5.2%[17]. But, in the finding (Abalos et al., 2014) is higher than the global prevalence [18]. This difference might be due to socio-cultural, variability in maternal risk factor distribution, and the difference in antenatal care service accessibility. In addition, most of the studies included in this meta-analysis were conducted in hospitals and health centers which might increase the prevalence

Young maternal age was not associated with Health Disease In Pregnancy. Similar finding was also observed in a systematic review on pre-eclampsia. The study showed that young maternal age doesn't affect the risk of developing pre-eclampsia [19]. But, other studies showed different findings in the occurrence of Health Disease in Pregnancy among younger and older mothers.

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# *Dynamics of Thyroid Gland Dysfunction*

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## Abstract

*Following the cessation in our country of the incidence and prevalence of endemic goiter because of the widespread use of the iodized salt by the albanian people, in the foreground it is now resulting in the more frequent occurrence the impaired thyroid function due to the autoimmune Hashimoto's thyroiditis*

***Aim of the study**: To compare the prevalence of endemic goiter in the population of Gjirokastra County following the use of iodized salt and current diseases of the*

*thyroid gland with impairments of its function such as autoimmune thyroiditis, and to promote early diagnostic and therapeutic activities towards it such as ultrasound screening of the thyroid or cases with pseudo nodes stria, TSH and ATPO examinations, in particular cases anti-Tg and IgG + IgM EBV, nutritional therapies and medications to stop progression to hypothyroidism.*

***Key words:*** *Goiter, endemic Goiter, Thyroid, TSH, ATPO*

## Methodology

This study was based on cases presented at the polyclinic in one of the endocrinology cabinets in Gjirokastra with complaints of thyroid pathology. After clinical examination and ultrasound, laboratory examination was required for suspected cases: TSH, ATPO; unclear cases and anti-TG, and IgG + IgM EBV.

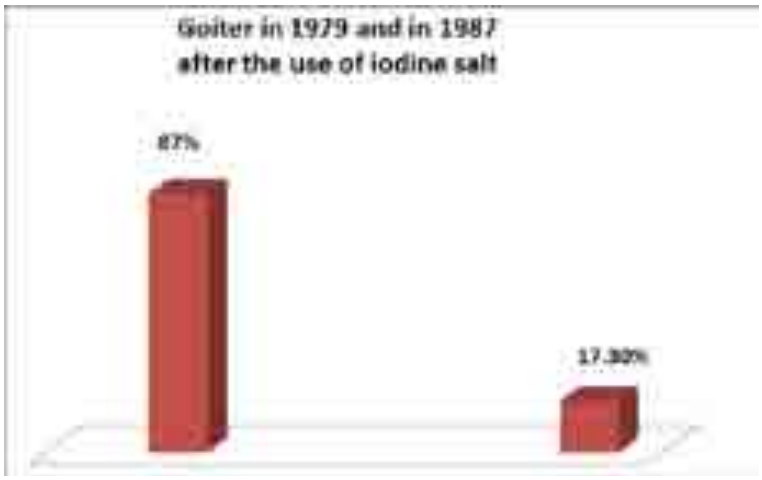
## Content

The goiter or struma is an increase in the volume of the thyroid gland that is followed by the disorder of its function. The disease is common but in developed and high standards countries, thanks to the use of iodized salt, it is not problematic anymore. Morbidity depends on the amount of iodine in the soil, where iodine is adequate, livestock products such as milk, meat, etc. will have the necessary amount of iodine, as opposed to foods obtained from poor soil iodine, where struma will be more frequent. The soil is enriched with iodine from the rains coming from the sea, consequently, old soils will have more iodine in the geological sense than new soils.

## Historical aspect

We first undertook a study of endemic goiter propagation by Prof. Fejzi Hoxha who presented this data in 1976 in his book called "Endemic Goiter". In 1977-1979, In the district of Gjirokastra, endemic goiter screening was undertaken by the health center (started in 1977 and ended in 1979). A study was carried out that continued until 1997 on the epidemiology of goiter and its prophylaxis with iodized salt (Vlora iodized salt). This study was conducted by Dr. Hodo Celo, controlled by professors of the Faculty of Medicine - Prof. Fejzi Hoxha, Prof. Isuf Kalo and Prof. Hektor Peci. 88.1% were found in the Lunxhëri area from Odria to Libohovo at 6-15-year-olds, while in the areas opposite to Gjirokastra such

as Lazarat-Dropull there is an average of 22%, and in Picar area was around 5%. Since 1979, the iodine salt of Vlora has been traded in the area of Lunxhëri and for 8 years the frequency of goiter in Lunxheria has decreased to 17.3% in 1987. From the use of iodized salt, there has been a drastic decrease in the incidence of goiter. Even the study in animals (in kids) in Erind (Lunxhëri) where iodine in water was 2.5 gm / l average weight of thyroid gland in kids (immature goats) was 1195.83 mg, - in Picar area where iodine in water was 6.8 gm / l the median thyroid gland was 728.4 mg. The high weight in Lunxheria kids, indicates that animals also suffered from struma.




## Discussion

At present, when they do a medical check-up, patients rarely come with complaints of struma, and we no longer find strumas with prominent deforming neck nodes as before the 80s. Cases of solitary nodes or cystic nodes are now reported. In the cases presented today for complaints from the thyroid gland, thyroiditis, especially Hashimoto's thyroiditis comes first that are followed by hypothyroidism and less frequent is Basedow disease hyperthyroidism.

We mentioned these because autoimmune thyroiditis and Morbus Basedow are more common in areas with iodine and in the areas with iodine rich foods consumption than in areas with iodine deficiency.

Even in our district of Gjirokastra, where it was endemic after its dominance through iodized salt, cases of autoimmune thyroiditis increased.

There is no previous study related with that (on autoimmune thyroiditis) for reasons also related to the impossible diagnosis. However, currently, cases of autoimmune thyroiditis are often observed by cases that go for an endocrinologic visit, not from any screening which was not possible, but which is required. Our findings suggest that family links to autoimmune thyroid disease are frequent.

*Cases with autoimmune thyroiditis are not as high as endemic goiter (which used to be higher) but Hashimoto's autoimmune thyroid disease is more invalidating given that it causes 90% of hypothyroidism adding here also most morbus Basedow cases; and maternal and fetal consequences during pregnancy, etc.*

The pregnancy causes marked modifications of the thyroid function in the mother, aggravating or favoring hypothyroidism, especially in the case of iodine deficiency or autoimmunity. Hypothyroidism in pregnancy is associated with a risk of complications for the mother and the fetus such as abortions, and delays in the child's psychomotor development. The gravity of these complications depend on the gravity of the hypothyroidism, and especially on the quality of the mother's treatment during pregnancy., etc. Such screening is not practiced *en masse* for reasons of economic cost but selected in cases where we have suspected it. For the damage it causes to the mother and to the fetus it is worth putting in the protocols during and after pregnancy ultrasound of thyroid, ATPO and TSH.

## Findings

In the last two years, the endocrinology cabinet has identified cases of autoimmune thyroiditis primarily by ultrasound screening of the thyroid and in suspected cases thereafter we have regularly sought TSH and ATPO in specific cases of ATG and IgG, IgM Epstein Barr virus.

The following is a comparison table of cases with autoimmune thyroiditis.

Comparative data of TSH, ATPO, and ecographic aspect

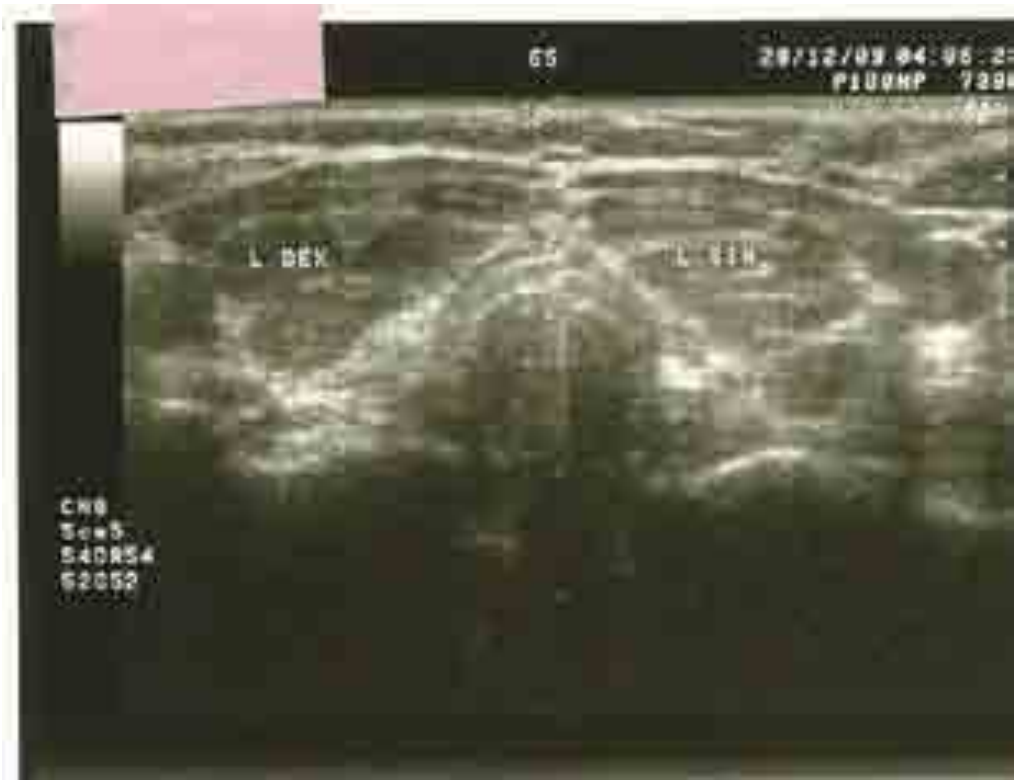
| Total | TSH | | | ATPO | | Ecographic aspect | | | |
|---|---|---|---|---|---|---|---|---|---|
| | high | low | normal | high | normal | Pseudo Node multiple | Butterfly shape Hypoechogene-etnicitet | Irregular Hypoecho-gene-etnicitet | izoekoene |
| 313 | 113 | 38 | 162 | 301 | 12 | 222 | 39 | 46 | 6 |

In this study, 313 cases of autoimmune thyroiditis (these in only one endocrinology cabinet at the polyclinic) were reported in 113 cases with elevated TSH, 38 cases with decreased TSH, and 162 with normal TSH. This statistic does not include cases that were verified with Morbus Basedow. Cases of high TSH have been interpreted for hypothyroidism and generally had clinical signs. Cases with decreased TSH, high ATPO, and pseudonode were interpreted as Hashitoxicosis. Normalization was seen in recent dynamic follow-up cases of TSH or its increase.

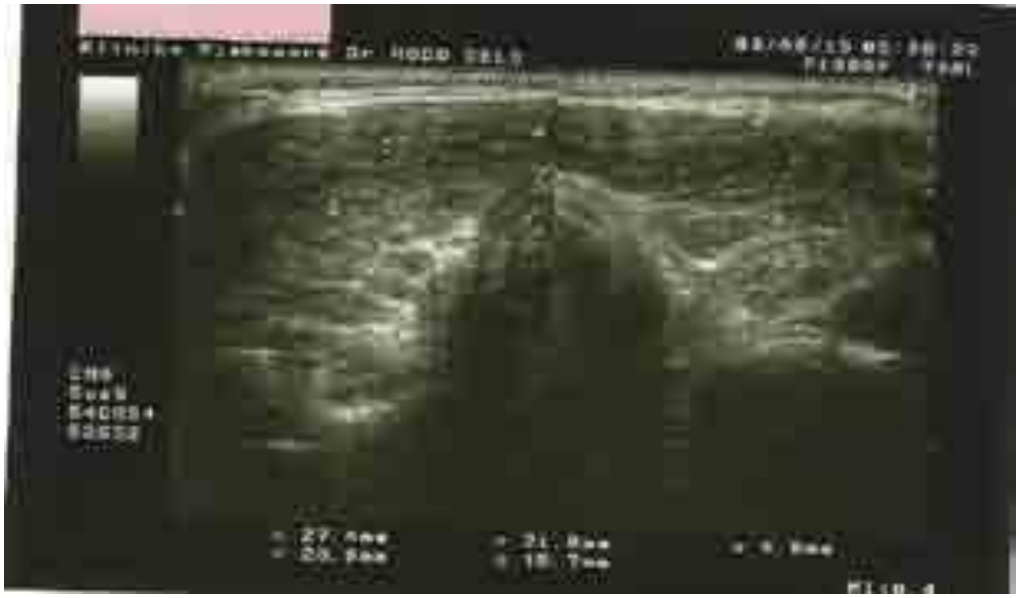
Anti-peroxidase antibodies (ATPO), except for 12 cases that were isoechogenic, the others had had abnormal decreases in echogenicity (pseudonode) in ultrasound. This result suggests the selection of cases by ultrasound (which is usually performed by many researchers).

There were 79 cases of stria generally in those with hypothyroidism, indicating the late capture of cases where connective tissue developed in the affected areas.

Fibrous stria



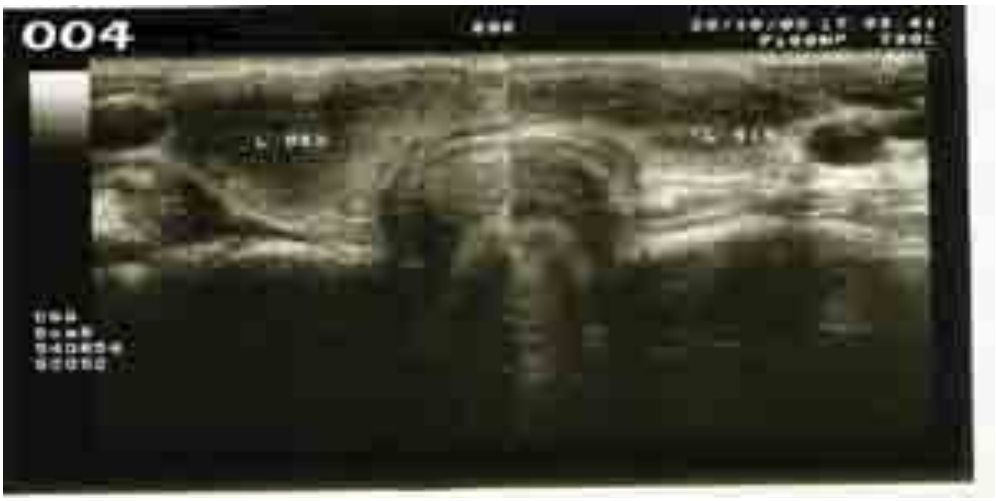

Pseudo node and fibrous stria

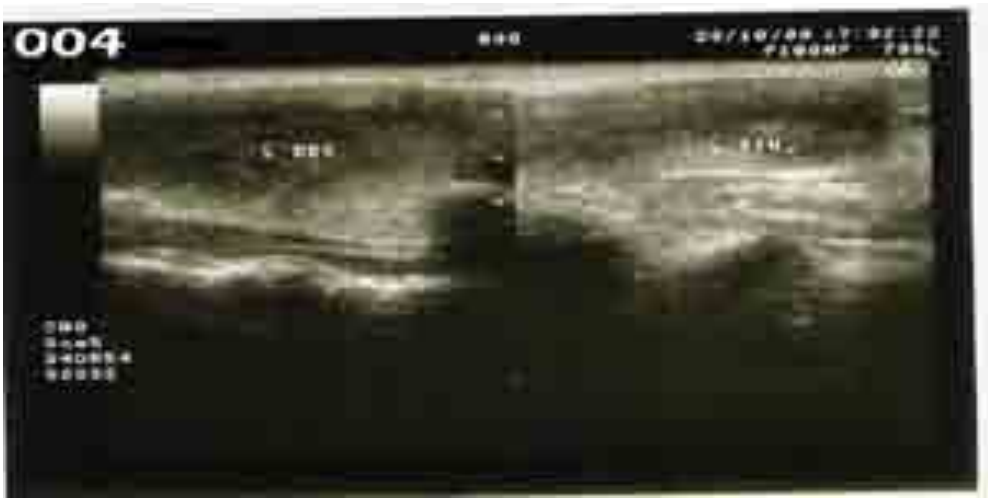


Ultrasound data: heterogeneous hypo echogenicity, irregular shapes, by radiologists are called pseudo nodes. Some radiologists simply describe them as nodes without describing their irregularities and whether or not they have limitations (halos). The latter are of interest to the clinician to differentiate between genuine

Extensive hypo echogenicity

Butterfly shape hypo echogenicity

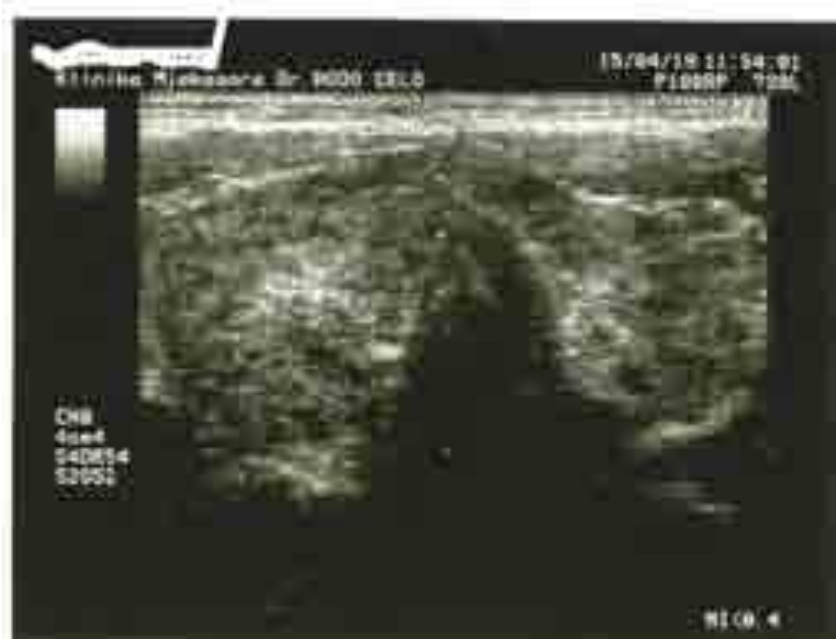


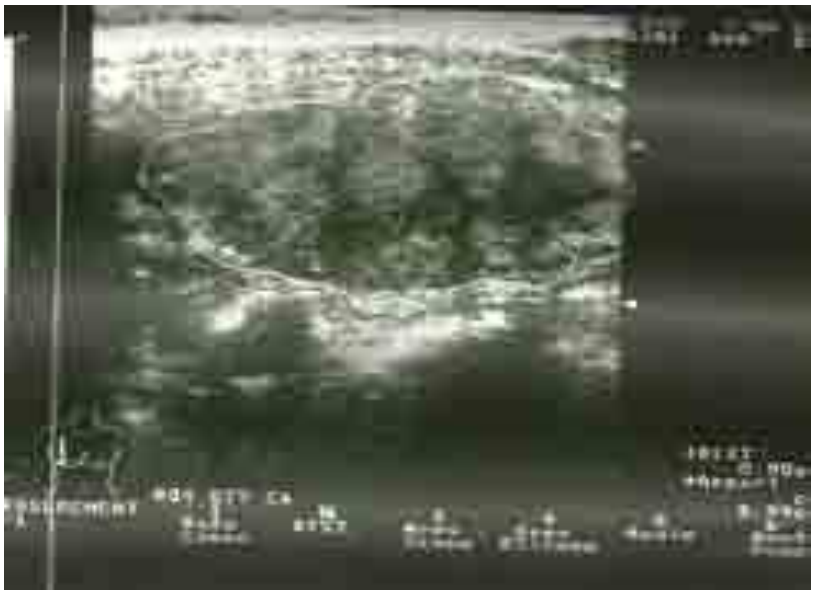
nodules (including cancer) and pseudo nods. In fact, in mild thyroid palpation, no nodes are found, it is mobile, in ultrasound shows large or small hypoechogenic areas. In some of them, there are non-regular, halo-free, hyper echogenic zones. We have multiple pseudo nodes such as beehives or leopard skin. Pseudo Micronodules or multi microcysts (the latter is rare) when multiple are described as pseudo-nodules. We can find rare pseudo nodes in the lobe or in one lobe.

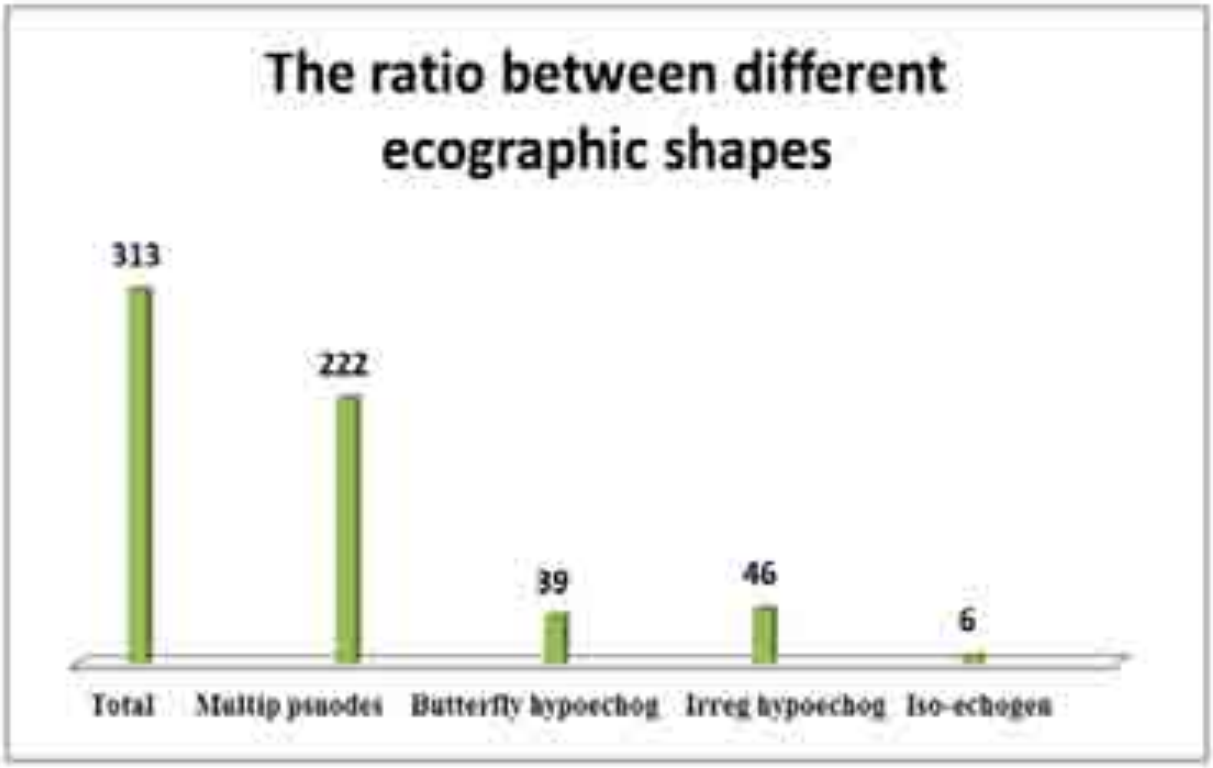
On different shapes, we have encountered stretches in one part of the hypo echogenicity lobes, or we may find them symmetrical in the shape of a butterfly in both lobes, and in the form of multiple pseudo nodes.

Multiple Pseudonode



With hypoechogene and hyperechogene pseudo nodes






In the cases with pseudo nodes, 222 cases had multiple pseudo nodes; in 39 cases in a butterfly shape, 46 cases with irregular hypoechogenic areas of different sizes and only 6 cases thyroid was iso echogenic. The latter cases were assessed by the clinical findings and TSH; ATPO in special cases also anti-TG.

## Recommendations for following the treatment

To use:

1. Gluten-free diet excluding any foods with wheat, rye, barley, and oats.
2. Selenium
3. Zinc
4. Probiotics
5. In most cases for helicobacter pylori - with Flagyl (metronidazole), etc.
6. Spirulina especially when we have data on the active or dormant presence of Epstein Barr virus by doing IgG and IgM assays — Epstein Barr virus.
7. In cases of hypothyroidism with levothyroxine continuous follow-up is important. In cases of normal TSH, it is not applied, in order to allow the thyroid to compensate for the deficiency itself.

In most cases with this medication, the dynamics have been good. The purpose of treatment and diet has been to stop the immune activity and not to continue damaging the tissue. Cases of hypothyroidism should stay at the same level as not to go into the myxedema.

## Conclusions

1. The prevalence of endemic goiter in Gjirokastra district was reduced due to iodized salt. Visits to our endocrinology cabinet point out that at the forefront of thyroid diseases are thyroiditis, especially Hashimoto's autoimmune thyroiditis, followed by Hypothyroidism (90% of which is Hashimoto's thyroiditis) and Morbus Basedow.
2. Ultrasound findings suggesting for Hashimoto's thyroiditis also serve as screening, in all cases that result in Hashimoto in the ultrasound, you require tests such as TSH, ATPO, aTg, and IgG-IgM-Epstein barr virus. It is noteworthy that there is a high concordance between ATPO and the ultrasound.
3. Being unable to perform a mass screening is suggested as follows:
   a. Ultrasound of thyroid, TSH, ATPO and in special cases IgG, IgM, Epstein Barr virus to be in the protocol during the pregnancy and postnatal examinations up to 18 months
   b. Request TSH, ATPO, and ultrasound in all cases of hypothyroidism.
   c. These TSH, ATPO, Ultrasound examinations should be performed for all autoimmune diseases like type 1 diabetes, rheumatoid arthritis, etc.
   e. These examinations should be performed to all patients presenting with thyroid dysfunction.
   f. These screening tests should be performed on the entire family of patients with Hashimoto Autoimmune Disease. These examinations should be done to all patients with muscular and articular pain, especially in winter, when rheumatologists have not concluded for any pathology.

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# *Cardiac Arrest in Anesthesia*

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## Abstract

*Aim of this study is fast Recognition, Management of situation of Cardiac Arrest during Anesthesia and treatment of complications. Objectives are: Analysis of Causes that trigger Cardiac Arrest, analysis of risk factors and prevention of Cardiac Arrest in Anesthesia. Is known that Cardiac Arrest occur at 0.5/ 10.000 cases of Anesthetized Patients. Between other Causes, Human Mistake is one of cause of Cardiac Arrests. Cardiac Arrest can be defined as an physio-pathologic situation of acute Cardiac failure ,when the Heart stop and can not supply with blood -vital organs, mainly the Brain. Causes of Cardiac arrest are multiple and more important are: Cardiac arrest with Reflector origins, direct cardiac trauma, overdose of anesthetic drugs, Ventricular Fibrillation, acute coronary failure, acute diminished venous reflux, cardiac arrest from metabolic disorders, massive blood transfusions, anaphylactic reactions and cardiac arrest from special surgical procedures as prosthesis with implanting cement. Symptoms during Anesthetized patients are poor, but Anesthesiologist must be very careful. Symptoms are, hypotension, cyanosis, disrythmia, hypoxia, hipercarbia, surgeon see `black blood`, and asystolia. Mydriasis occur r 45 sek after Cardiac Arrest and is in fact a late symptom of Cardiac Arrest during Anesthesia. Cardiac Arrest con cause within 2-4 min irreversible changes, that can cause death or permanent grave neurologic and psychiatric inabilities. Treatment must be emergent within 20-40 sec after Anesthetist has diagnosed Cardiac Arrest and must include Interruption of surgical Operation, change of position of patient in surgical bed, interruption of Narcotic agents, giving of Oxygen 100%,careful cardiac monitoring, and starting of CPR. The predetermined objectives are: Analyzing the causes of cardiac arrest under anesthesia, Analyzing the risk factors of cardiac arrest in anesthesia, Prevention of cardiac arrest under anesthesia, Treatment of Cardiac Arrest During Anesthesia,*

*Discuss the role of the Protocols in cardiac arrest management. Terapeutic Principles are: Phase of CPR, Phase of Patient Ventilation and careful Monitoring, Fase of Diagnosticcation and Intensive Care Therapy.*

***Key words**. CPR, Anesthesia, Cardiac Arrest, Monitoring, BLS- Basic Life Support, ACLS-Advanced Cardiac Life Support. CPR-Cardio Pulmonary Resuscitation, AED-Automated External Defirbrilator.*

## Incidence of Cardiac Arrest under Anesthesia

- Cardiac Arrest in General Anesthesia 0.5 / 10,000 Anesthesia occurs, in the US in 20 anesthesia performed -1,000 patients per year under cardiac arrest during Anesthesia, or 3 patients daily.
- In Neuro-axial Anesthesia, Cardiac Arrest during Anesthesia occurs in 1.8 per 10,000 patients, but most occur in Spinal Anesthesia 2.9 / 10,000 than in Epidural 0.9-10,000 patients.
- Hypoxemia is not charged more than high spinal anesthesia. as well as the selection of vasopressors in these cases (Anesth Analg 2005; 100: 855-865).

One statement to keep in mind is the Muray phrase that says: `` Human error is one of the major causes of Cardiac Arrest during Anesthesia, but the structural complex of the recurring human error, formerly called the 'chain of accidental evolution', challenges it even the most successful strategies` (Murray DJ, 2004).

## Epidemiology of Cardiac Arrest under Anesthesia

- The Epidemiology of Cardiac Arrest under Unique and Special Anesthesia. Managed 518,294 patients with Cardiac Arrest during Anesthesia (Mayo Clinic in Rochester, Sprung J, et al. 2002).

Cardiac arrest due to dysrhythmia and hypoxemia is rarely observed when good monitoring, sedation, and general or regional anesthesia are provided.

- During the Anesthesia, it is important to have proper recognition and current diagnosis, which lead to successful management.

Cardiac arrest can be defined as a cardiac arrest causing an acute inability to maintain sufficient Cerebral circulation.

## Causes of Cardiac Arrest in General and During Anesthesia

### *1.Arrest Reflector due to vago-vagal stimulation*

Vago-vagal stimuli are induced by

- surgical trauma in the Aorta region,
- Hilus Pulmonar,
- flexion during traction,
- the carotid sinus
- when the vagus nerve is cut.
- anesthetic procedures such as Intubation, Tracheobronchial Irritation,
- immediate movements to position the patient

### *2. Direct Trauma to the Heart such as*

- Cardiac operations in the pericardium,
- Cardiac operations,
- Pressure of the diverticula (retractor) on the heart or aorta

### *3. Overdose of anesthetic substances which depress circulation*

- through the direct effect on the heart by depressing the myocardium (such as Chloroform, Chlorethylene,

Cyclopropane, which is not used or used today, as well as anesthetic substances inhalers that give hypoxia

- by vasodilatation as, anesthetic I / v.

### *4. Ventricular fibrillation due to adrenaline release*

- By endogenous pathway in case of excitation of adrenal glands a large amount of adrenaline is released,
- During an inappropriate, light anesthesia, adrenaline is released which causes ventricular fibrillation

*5. Arrest originating from coronary insufficiency: (high risk at waking time because heart rate increases)*

The drop of Pa02 with only 20 mm Hg, creates major disturbances.

- Excessive analgesic effect after surgery, aches and pains begin to increase, post-cardiac output increases, T / A increases and consequently, rhythm disorders that precipitate cardio-circulatory arrest from hypoxia begin, and greater oxygen demand in the immediate postoperative period

*6. Arrest of decreased venous reflux*

- usually occurs in hypovolemic patient,
- In patients who have suffered asphyxia,
- In patients with respiration directed to PEEP,
- We hypovolemic patients even while changing their position in bed brusquely

*7. Arrest from metabolic disorders*

- An accidental excess of potassium,
- After giving i / v to miorelaxin (which increases potassium to 12 mEq / l, gives Asistol, but there are no signs of hyperkalaemia in ECG because it occurs very quickly),
- In metabolic acidosis (shock, politrauma, oligo-anuria, mass transfusions, because toxic metabolites and inorganic acids (from anaerobic metabolism) accumulate, which are not eliminated in a timely manner.
- It may also occur from Hypokalemia during expressed alkalosis

*8. Arrest from the introduction of ischemic territories into the systemic circulatio*

- High relief, who stayed for a long time (over 75-90 minutes) from the lower extremities in orthopedics, when there were snake bites on the leg and the patient was transported to the hospital for a long time),
- Crush-syndrome. Due to the introduction in a very short time of a large amount of toxic metabolites, as well as of inorganic acids produced by anaerobic metabolism, such as lactic acid, pyruvic acid)

*9. Arrest by mass blood transfusions*

- occurs due to the introduction into the blood of the recipient of citrate, which binds plasma calcium giving Hypocalcemia,
- but cold blood may also occur, which immediately lowers body temperature by several degrees causing cardiac arrests and arrests, if no measures are taken.

*10. Cardiac arrest by anaphylactic reactions*

- from peripheral vasodilatation that reduces venous reflux by giving circulatory collapse.
- from hypoxia caused by bronchospasm (due to an increase in histamine, bradykinin by an anaphylactic reaction),
- by the direct action of the antigen-antibody complex on the heart

*11. Cardiac arrest in special operations such as*

- Cement Properties during the placement of Femoral Head Prosthesis in Orthopedics,
- manipulation of the Spermatic Cord,
- manipulation of fractured femur,
- broken amniotic membranes.
- Electroconvulsive therapy

## Physiopathology of Cardiac Arrest

Cardio-circulatory arrest is a physiopathological condition where the heart cannot supply blood to the vital organs (Brain, Heart, Pulmonary). The factors are many like:

- Hypoxia PaO2 <20-50 mmHg, PaCO2> 60 -100mmHg,
- Collection of toxic metabolites and acidic substances through anaerobic metabolism such as Lactic acid, Pyruvic acid, NH4 + ions.
- The Cardiac Arrest under Anesthesia is divided into three groups of Factors:
- Intra-operative hemorrhage

Pre-existing cardiac pathology

- Acute hypoxia. Disorders that occur in General Anesthesia and Neuro-Axial Anesthesia (regional) are:
  - Bradicardia that continues up to asystole (45%),
  - Ventricular tachycardia and ventricular fibrillation (14%),
  - Electric activity without pulse (7%),
  - Lack of 33% heart rate (heart rate is not fully documented).

## Patogenesis

Cardio-circulatory arrest that occurs during anesthesia:

- It is benign and returns in 70% of cases.
- The myocardial reserves are for 12 systoles only: then heart dilation occurs;
- Pa02 <60 mm Hg has rhythm disorders;
- Pa02 <50 mm Hg bradycardia occurs.
- Pa02 <30 mm Hg, heart enters lethal threshold.
- PaC02> 90 mm Hg + Halotan, has rhythm disorders.
- PaC02> 100 mm Hg Cardiac arrest occurs.

Hypoxia also occurs when the HB02 dissociation curve crosses the right and oxygen is not absorbed by the tissues.

## When Cardiac Arrest Anesthesia Occurs

- During the Perioperative Period The patient in a `sudden ‘manner receives Pulse Arrest without pulse for a period of several minutes - up to several hours.
- This requires taking aggressive and aggressive measures using ACLS (Advanced Cardiac Life Support) in the Operating Room.
- Cardiac arrest can cause irreversible changes within 2-4 minutes

## Some features of Cardio-Circulatory Arrest

Cardio-circulatory arrest occurs immediately after the above-mentioned symptoms:

- The respiratory arrest may come shortly after 20-60 seconds after cardio-circulatory arrest;

Cardio-circulatory arrest arrives immediately after 3-5 minutes after respiratory arrest.

- Deep coma occurs after 4-8 seconds after cardio-circulatory arrest.
- Midriasis is a late sign of cardio-circulatory inhibition because it occurs after 45 seconds to 1 minute and 45 seconds.

Immediately after Cardiac Arrest: Acute brain cell suffering begins immediately in the brain: When PaO2 <50 mmHg, PaCO2> 60 mmHg of brain occurs:

- Massive cerebral glycolysis,
- After 3-5 minutes.trom diffuse cerebral artery boils with cerebral necrosis arise.
- Over 3 minutes and 10 seconds, brain function can return without any subsequent disturbance.
- The inhibition lasts 3 minutes and 30 seconds, then the patient will notice psychic changes.
- When Arrest lasts up to 6 minutes, it leaves disorder and appearance changes
- When the Arrest lasts over 7 minutes, the brain dies.
- This time may decrease in hypoxemia and may increase if the patient is anesthetized or the patient is at low temperature.

## The Cardio-Circulatory Arrest Warning Signs are

- Circulatory arrest does not come unexpectedly,
- The anesthetist must be very attentive,
- Every detail is evaluated by asking: Why is this symptom occurring?
- Warning signs are few,
- bradycardia,
- T / A movements,

- cyanosis
- rhythm disorders,
- lack of peripheral pulse,
- very rare carotid pulse that is extra-ventricular systole,
- Dark (black) blood in the surgeon's operative field
- ACLS Cardiac Monitoring Data:
- pulse-free ECG (ventricular tachycardia or ventricular fibrillation),
- Pulse loss x 10 seconds
- End-Tidal Loss of CO2
- Loss of the plethysmograph

## Following on from the Cardio-Circulatory Arrest Clinic we can conclude that

Cardio-circulatory arrest is not diagnosed quickly when the patient is under the anesthetic effect, when the patient is not monitored.

There may be confusion at first, but CPR should not be delayed. CPR in the operating room should begin within 20-30 seconds of diagnosis. CPR is also initiated if the doctor is not fully convinced, whether or not he is under arrest. The patient with Arrest Cardio Circulatory (clinical death) should always be treated with CPR even in the operating room.

## Cardio - Vascular Arrest Diagnosis

In Anesthesia it is problematic and depends on a careful and efficient evaluation by the Anesthetist

(minor) symptoms that occur during Anesthesia depend on the changes in the ECG rhythm,

Oxygen De-saturation, Capnography Level, Sufficient Monitoring, Respiratory Depression, Condition of Consciousness in the Awakening Room or During Local and Regional Anesthesia.

## Differential diagnosis can be made by

- Hypoxia from Trauma / hypovolemia,
- Hypovolemia from Pneumo-Thorax Valvular,
- Hyper-vagal coronary thrombosis,

- Tamponade of Hydrogen Ions,
- Hypokalemia from Thrombus in Pulmonary Artery,
- Prolonged `QT 'syndrome in Malignant Hyperthermia,
- Hypothermia due to toxins (anaphylaxis),
- Hypoglycemia during Pulmonary Hypertension

## Immediately treatment

Once diagnosed by the Anesthesiologist & Resuscitator, the primary surgeon is immediately notified of the surgery; Stop Blood Loss, Put Patient in Horizontal Stretch Position, Expose Thoracic, Non-Gestational Head, Give Precordial Blow, and Start External Cardiac Massage 30/2, (or 100 / min), Ventilate Patient with 100% O2, in Anesthesia Case Emergency Regional - Intubate the patient, Careful ECG monitoring to ascertain: bradycardia, asystole, tachycardia and fibrillation.

Provide a correct dose of Adrenaline i / v, heart injection, or electric syringe,

- Liquid supply i / v,
- Use of Atropine in bradycardia,
- Use of Lidocaine in Ventricular Tachycardia,
- Defibrillation with AED,
- BLS (basic life support) extension
- Preparation of other medicines:
- Symptomatic Agonist Medications: Metaraminol, Dopamine, Noradrenaline, Isoprenaline,
- Bicarbonate as Sol NaHCO3 8.4%,
- Beta blocker Atenolol,
- Beta2-stimulants such as Salbutamol,
- Cortisone like Hydrocortisone, Dexametazon
- Aminofilini,
- Arteriolo-venulo dilator as Lenitral.
- Naloxon, Magnesium Sulphate, Prochlorperazine

## BLS / ACLS in the Operating Room

CPR for Patients Under Anesthesia Doesn't Begin With '.. Hey, Are You Good…?

- Install relevant personnel to start an effective CPR,
- Continue Anesthesia and Surgery,

- Keep AED (defibrillator),
- Ventilate with Ambu if the patient is not intubated but intubate immediately with FiO2 = 1,
- Don't stop CPR! Capnography is a more reliable indicator of the resumption of spontaneous circulation than the palpation of a. carotid, or a.femoral,

Manually ventilate at 8-10 ventilation / min with 1 sec Inspiration, and with O2-100%,

- Evaluate if there is obstruction: if -no, start mechanical ventilation, if-yes, obstruction-aspiration, fibrobronchoscopy,
- Continue CPR,
- Keep all roads open.

## Cardio-Circulatory Arrest Management for Specific Causes

In case of suspicion of occlusion of the inferior vena cava in the operation of the uretero-litho-tomoma the operating table should be directed which in this case is placed in a separate position.

Emergent thoracotomy should be performed in the case of Pulmonary Embolism and in the case of a Thoracic rupture (in order to provide upper respiratory tract).

Lower head, used in the case of gas embolism,

- Autonomous stimulation may be interrupted in the case of:
- traction of the extra-ocular muscle,
- traction of muscle and release of CO2 from peritoneal cavity.

## Specific treatments through ACLS

ACLS- Advanced Cardiac Life Support; -It is known that: in a state of reduced flow, prolongation of increased thoracic pressure is proportional to Ventilation rate and inverse, is proportional to T / A, and Coronary and Cerebral perfusion.

- Lower levels of ventilator support are recommended because, Ventilation at 20 respirations / min is associated with lower survivance than ventilation at 12 respirations / min, thus using negative pressures during ventilation.

## Cardioversion. Special considerations

Immediate cardioversion for the patient with serious signs associated with tachycardia, or when ventricular rhythm> 150 min,

- Always be prepared for patients with transcutaneous pacing who have undergone cardioversion to convert them to deep bradycardia.
- Biphasic Defibrillators (AEDs) are more effective than Monophasic ones,
- The combination of Vasopressin with Adrenaline (together), is more effective than their individual use.

1. In penetrating traumatic injuries, Open Heart CPR is recommended as an optional treatment to improve% of survival. It is important that this procedure is started as soon as possible and at least within 20 minutes of starting the standard CPR.
2. In closed trauma cases the outcome was the same.

(J Trauma. 2004 Oct; 57 (4): 809-14. «Open-chest cardiopulmonary resuscitation after cardiac arrest in cases of blunt chest or abdominal trauma: a consecutive series of 38 cases»).

## Therapeutic Principles

1. The first phase or the phase of artificial respiration + cardiac massage (30/2) at the scene and during transport,
   - the cause is not yet known exactly,
   - continues until the restoration of the central and peripheral pulse and spontaneous respiration, normal coloration of the skin, normalization of the pupils and gaining consciousness.
2. Second stage or ventilator phase:
   - continues in the hospital, where artificial respiration and cardiac massage continue while monitoring the patient (with cardiac monitor + defibrillator alert),
   - adding oxygen and bringing the patient into mechanical ventilation,
   - alkalinizing the patient,
   - adding vasopressors.
3. Third phase - the phase after the patient is diagnosed,
   - continues in Reanimation,
   - What kind of Cardio-Circulatory Arrest it is. The diagnosis is based on the therapy,

All three phases are performed continuously and dynamically, which are not substantially different from CPR measures.

## Extreme Care

- Confirm and correct the Cause,
- Treat Anaphylaxis and Septicemine,
- Prevent and correct Hypothermia,
- Regulate the patient's admission to Resuscitation,
- Document the event carefully as soon as possible.

## Cardiac Arrest Post Care

- Care has the significant potential to reduce Early Mortality caused by Cardio-vascular instability, and later by Morbidity and Mortality due to Multi-Organic Insufficiency and Brain Damage.
- Post-Cardiac Arrest Care after returning to cardio-vascular-spontaneous circulation rates can improve patient survival with a good quality of life.
- Check temperature to optimize survivance and neurological healing,
- Identify and treat Acute Coronary Syndrome,
- Optimize mechanical ventilation to minimize pulmonary damage,
- Reduce the risk of multi-organ damage and improve organ function,
- Objectively evaluate the healing prognosis,
- Assist survivors through Rehabilitation services when required.

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# *Bad medicine from the uses of wrong procedures*

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## Abstract

*Cases of bad medicine by using wrong procedures have been numerous due to lack of medical knowledge, despite the efforts of doctors to cure diseases. According to scholars David Wootton and Nathan Belofsky, these cases have been encountered since ancient times.Doctors, scientists, and thinkers who introduced wrong theories and involuntarily injured people during the treatment of their illness were not charlatans, but well-known doctors, the leading medical figures of their time. At present, medicine has been introduced to the right path of its development, alleviating pain and curing many illnesses, which has made it possible to increase the life expectancy of humans. However, even in today's and the most advanced medicine of the future, which are the direct inheritance of previous medicine, sometimes bad medicine cases by using the wrong procedures are encountered. In Albania since the 1990s, with its opening after a long isolation, the possibility was created to apply world biomedical sciences achievements, but also the bad and forbidden medical practices of developed countries. The author analyze a medicolegal case in Albania involving the misuse of cancer treatment with sodium bicarbonate from an Italian physician. It is necessary that relevant institutions, strengthen the control and legislation concerning the work of foreign doctors in Albania to prosecute these cases and avoid medical malpractice.*

***Key words:*** *Bad medicine, Wrong medical procedures, Albania, Italy*

## Introduction

Cases of bad medicine by using wrong procedures have been numerous due to lack of medical knowledge, despite the efforts of doctors to cure diseases.

According to scholars David Wootton and Nathan Belofsky, these cases have been encountered since ancient times. Doctors, scientists, and thinkers who introduced wrong theories and involuntarily injured people during the treatment of their illness were not charlatans, but well-known doctors, the leading medical figures of their time. (Belofsky 2013 and Wootton, D. 2006).

These wrong procedures, including the use of magic, blood loss (salasso), rotational movements of the mental sick persons, and many others, have remained hidden for a long time, buried in the piles of old books and documents.

## Some historical data on bad medicine

Some of the most prominent cases of bad medical practice during the past centuries (Belofsky 2013, pp. 1 - 90), are as follow:

-***In ancient Babylonia*** (Belofsky 2013, pp. 2-3), in archaeological materials: clay tablets fortuitously baked to stone durig a fire, it turns out that the illnesses were treated there by the collaboration of magicians called *asipu* and doctors, the *asu*, but the *asipu* had the greatest value.So they believed some illnesses were caused by the disturbances occurring to humans by gods and demons and others from a person's own bad behavior.For their treatment, they advised, among other things, placing special signs in the sick's home, such as, for example,putting on a pig's tail, or having a soothsayer drink the so-called "magic drink" shot in a leather bag, where also the hairs of a black dog and a cloth dampened with the menstrual fluids of one woman.

Another treatment was carried out by placing around the neck of the diseased manure made from fecal matter of pigs; or for dental diseases: the sick person had to sleep for seven days near a human skull and kiss it seven times each night.

-***In Ancient Egypt***, in Smith's papyrus, it was noted that scalp was treated with fresh meat; in Kahun papyrus: they were treated by rubbing the eyes of the patient with the fat of the goose together with the liver of a kind of monkey. At a person with a toothache it was put a dead mouse in his mouth and throat (Belofsky 2013, pp. 4 - 5).

-***In Old Greece*** they thoght that the world was made up of earth, wind, fire and water; the art of cure required that these elements be kept in equilibrium through diet, meditation, and exercise (Belofsky 2013, pp. 5 – 8).

-***In Old Rome***, the historian Old Plin, for his toothache, advised as a medication, among other things, that the patient's mouth had to be rubbed with a tooth of hippopotamus and he had to eat the wolf's head dust (Belofsky 2013, pp. 8 - 10).

-***John Gaddesten,*** in the Middle Ages, in the 1300's, John Gaddesten, a doctor of medicine at Oxford University in England, incorrectly recommended, among other things, that before taking a trip, the man had to remove a quantity of blood ; for the cure of paralysis, boiling a dead dog was used; while for the poisoned children, their parents had to add to their food, without telling the children, meat of the goose; for the treatment of epilepsy he roasted a cuckoo and blew its powder up a person's nose; if it had no result, he would advise to hung the cuckoo's beak around his patient's neck (Belofsky 2013, pp. 20 -21).

-***Dr.Benjamin Rush*** (Belofsky 2013, pp. 94 - 96). In the late 1700s, Benjamin Rush, one of the signer of the US Declaration of Independence and the treasurer of the US Mint, was at the same time one of the most well-known doctors of the time.

He was considered the father of American psychiatry. But he mistakenly thought that psychic illnesses were caused by bad blood circulation in the brain, bad weather, the blood transfusion from animals to humans, etc.

For the treatment of these diseases, among others, he poured acid on his patient's backs and cut them with knifes; he kept these wounds open for many months or years, so that he would facilitate "permanent discharge from the neighborhood of the brain.

Another wrong method he used to do was to let the mentally ill without being fed, as he had heard that in Hindi, wild elephants were tamed through starvation.

In addition, he has recommended healing by the oscillation.For this, the psychic patient was strapped to chairs hung from the ceiling by a length of chain, which rotated for hours as a fugue, but that he did not use this method at the hospital.

But on the other hand, Dr. Rush has defended the human treatment of the mentally ill. At his hospital in Pennsylvania, he threw away the chains that kept them tied and treated them with love.

Today the seal of the American psychiatric society has the face decoration of Dr.Rush[1].

-***George*** **Washington** (Belofsky 2013, p. 116). An incorrect medication has also been applied to George Washington, the first US president in the period of his death. On December 13, 1799, he began to complain of sore throat and the next morning showed respiratory disturbances.

Immediately it was applied a blood loss (salaso) of about half a liter blood. Then they came to visit three of the best doctors in the country, and they did two bloodlettings of twenty ounces apiece.Finally another doctor came and he took blood again.

All of these actions were carried out over a period of eight hours, during which G.Washington was removed half of his blood volume. On 14.12.1799, at 10:10 p.m. he died.

-***Leucotomy and transorbital lobotomy.*** In 1939, the Portuguese psychiatrist Egas Moniz began performing the lobotomy or leukotomy operation in patients with psychiatric illnesses in Lisbon. For this, he drilled holes in the skulls of mentally ill people, and after that he destroyed the surrounding tissue around the side with alcohol and the wires that he inserted into the brain through this hole. In these neurosurgical interventions, the link of prefrontal cortex to the rest of the brain, was interrupted. Very soon this type of operation spread to all countries of the world, despite its poor results: high percentage of postoperative mortality, memory loss, various personality disorders, etc. (Çipi, B. 2005, Çipi, B., Meksi, S. - 2017 and Çipi, B., Çipi,S. 2015).

However, E .Moniz, for the discovery of this operation, was honored in 1949 with the Nobel Prize in Medicine.

But for his bad luck, one of his patients, apparently not fully convinced of the curative value of leukotomy, after threatening him several times, shot a firearm at the backbone, so he was paralyzed forever (died in 1955) (Çipi, B. 2005. p.121).

Another variant of this operation was that of American surgeon Walter Jackson Freeman, which was called transorbital procedure. Instead of dealing with skull drilling, used by Moniz, which was quite difficult, he entered in the brain directly through the eye hole.For this, he used ice picks, which he imprinted with a hammer and then rolled it many times after being inserted inside his head (Belofsky 2013, p. 177 - 178).

In the 1960s, these operations diminished considerably, as a result not only of objections from public opinion but also of the discovery of psychotropic medications. Currently, they are rarely carried out.

From the ethical point of view, the application of these methods is detrimental, because there is no scientific support, the results are very few, and the secondary effects are serious and sometimes have mortal consequences (Çipi, B. 2005. p.121).

## Actual situation

These are some of the cases of medical misuse of the past centuries, where doctors based on wrong theories have unknowingly harmed the sick. From the 20th century to the present time, medicine has entered the right path of its development, alleviating pain and curing many diseases and leading to increased life expectancy (Jackson, M. 2014 and Wootton, D. 2006).

However, it should not be forgotten that good medicine in our day and the still more advanced of the future is the direct inheritance of previous medicine (Belofsky 2013).

Thus, even today, sometimes cases of patient injuries are encountered until their deaths from the application of the wrong medical procedures

## Bad medicine in Albania

With the opening of Albania in the 1990s, after a long isolation, it was created the possibility that not only the achievements of world biomedical sciences to be applied in our country, but also bad and forbidden medical practice in the various developed countries, be transferred to use in our country.

This may also be due to the weaknesses that occur in the functioning of the respective national medical control links (Çipi, B. 2015 and Çipi, B.,Meksi, S. -2017).

***The medicolegal case of treatment of cancer with sodium bicabonate*** (Çipi, B. 2018. pp. 247 249).

Such an interesting example of the forensic medicine practice of our country belongs to the case of Italian doctor Tullio Simoncini, convicted and excluded from the right to practice the profession of doctor in Italy, because of the treatment with the baking soda which he had used for cancer in Italy and the Netherlands, had caused the death of some patients.

According to Simoncini, cancer is a fungal infection (candida albicans) that develops in an acidic environment, so Simoncini found the method of treatment by changing PH and consequently pretended to stop tumor development or treat it. For this purpose, he used high-grade solutions of high-quality baking powder. He has stated that this medication has been used for 20 years and many of his patients have been healed, even when other doctors predicted a mortal progress.

But his theory, unrecognized by medical science, is wrong, because the sodium bicarbonate introduced into the human body in large doses, disturbs the mineral balance significantly and causes the death of the patient, as were the cases with which he was condemned.On the other hand, this therapeutic procedure has not been subjected to experimental tests by scientific methods.

In 2011, this doctor, through cheating on the leading health instances of our country, was registered by the Albanian doctor's order as a diabetologist and oncologist for the account of the medical clinic "Our Lady of the Good Council".

In 2012, he applied to a private hospital in Tirana, his method of treatment of cancer, to an Italian 27-year-old Italian citizen who suffered from severe brain tumor illness. After carrying out the procedure of introducing the baking soda

in his body, the patient's health condition was exacerbated: headache, vomiting, minor epileptic attacks, until he died on the way to the CHU of Tirana.

The autopsy determined that his death had come from acute pulmonary edema in a person with a malignant brain tumor treated with sodium bicarbonate (baking soda).The case was considered by the forensic medicine and the Albanian prosecution as a careless medical case in the form of negligence, as this medication is not recognized by contemporary protocols, which led to the death of the patient. Albanian courts condemned the guilty doctor in 2015, imprisonment for a year and a half, and waiver of the profession's right for 6 months.

* * *

There are other cases of abuse of application of alternative treatment, such as cancer treatment with fish hook poison, according to a practice that has not been approved in the US and European protocols[5].

These cases indicate that, for the health of our country, among other things, it is necessary to strengthen the control by the appropriate instances for the admission of foreign doctors who practice our medicine, including the review by the ethics committee of the treatment protocols cases of use by foreign doctors of medical procedures that may be wrong[5].

Also, as proposed in 2017, the possibility to include in the penal code an article that foresees the punishment of the exercise of alternative medicine, which has had serious consequences for the patients without the appropriate authorization of the health authorities, should also be included[5].

## Conclusion

In conclusion, it should be noted that:

- The use of medicine, during almost all its history of development, has had many cases of misuse by using the wrong procedures due to lack of medical knowledge, despite the efforts of doctors to cure the disease.
- In the last 100 years, medicine has undergone proper development, affecting the healing and relief of diseases and increasing the life expectancy of humans, even today there are cases of medical misuse by the use of the wrong medical methods, as is the case of treatment of cancer with sodium bicarbonate in some European countries, including our country.
- In Albania, in order to avoid cases of alternative medicine by using wrong medical treatment methods from foreign doctors, it is necessary to strengthen

the control by relevant bodies, including the ethics committee, for the admission of these doctors to practice medicine as well as to strengthen the legislation on the punishment of such cases.

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# *Postmenopausal bleeding*

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## Abstract

*1.Preface: Menopause is defined retrospectively as the time of the final menstrual period followed by 12 months of amenorrhea. Post menopause describes the period following the final menses. Abnormal postmenopausal bleeding should always be taken seriously and be properly investigated, no matter how minimal or no persistent.*

*2. The Purpose: The purpose of our study is to determine what are the causes of postmenopausal vaginal bleeding and the percentage of endometrial cancer among other causes, diagnosis and treatment of these patient in our university hospital.*

*3. Methods: This is a retrospective study of clinical gynecological charts of 200 patients with diagnosis of postmenopausal bleeding from 1 January 2018- 31 December 2018 in the university «Queen Geraldine».*

*4. Statistical Analysis: We used IBM SPSS Statistics 25 test, Anova test, Spearman 'rho and Independent Samples test for processing these data.*

*5.Results The causes of postmenopausal bleeding we found: 55(27.5 %) of them had Hypertrophy, 20(10%) had Atrophy;38(18.5%) had Polips;20(10%) polipoid Fragments;65(33%) had endometrial cancer;1(0.5%) had cervical cancer,1(0.5%) atipic squamous cells. Age, menopausal age, years in menopause, endometrial thickness, HTA have a significant correlation with endometrial cancer. So we can say that these factors increase the likelihood of developing of endometrial cancer. I n our study we found no significant correlation between diabetes, obesity and endometrial cancer.*

*6. Discussion: Endometrial cancer takes the first place in our study because the gynecologist in the cities treat all benign cases and recommend to our university hospital all difficult cases like endometrial cancer.*

*7.Conclussions: Endometrial cancer is the most common cause of postmenopausal bleeding with 33 %.*

*8. Recommendation: We recommend a large prospective study to verify the percentage of endometrial cancer in Albania and to look for other factors that can contribute in the development of endometrial cancer.*

***Key words**: endometrial cancer, postmenopausal bleeding, menopause.*

## Preface

Menopause, the permanent cessation of menstruation caused by ovarian failure, occurs at an average age of 52 years, with a range of 40 to 58 years. Menopause is defined retrospectively as the time of the final menstrual period followed by 12 months of amenorrhea. Post menopause describes the period following the final menses. Despite a great increase in the life expectancy of women, the age at menopause has remained remarkably constant. A woman in the developed world will live approximately 30 years, or greater than a third of her life, beyond menopause. Therefore, it is important to ensure these years are as healthy and productive as possible. The age at menopause appears to be genetically determined and is unaffected by race/ethnicity or age at menarche. Early menopause describes menopause occurring between the ages of 40 and 45 years and occurs in approximately 5% of women. Premature menopause describes permanent loss of ovarian function before the age of 40, such as following bilateral oophorectomy. Primary ovarian insufficiency (POI) describes loss of ovarian function before the age of 40 years, which may not be permanent. POI occurs in approximately 1% of women. Abnormal perimenopausal and postmenopausal bleeding should always be taken seriously and be properly investigated, no matter how minimal or no persistent. About 90% of women with endometrial carcinoma have vaginal bleeding or discharge as their only presenting symptom. Endometrial carcinoma is the most common malignancy of the female genital tract, accounting for almost one-half of all gynecologic cancers in the United States .Endometrial cancer is a disease that occurs primarily in postmenopausal women and is increasingly virulent with advancing age. The definite role of estrogen in the development of most endometrial cancers is established. Any factor that increases exposure to unopposed estrogen increases the risk for endometrial cancer.

## The purpose

The purpose of our study is to determine what are the causes of postmenopausal vaginal bleeding and the percentage of endometrial cancer among other causes,

diagnosis and treatment of these patient in our university hospital. How obesity, hypertension, diabetes, age, menopausal age, years in menopause and endometrial thickness affects the endometrial cancer.

## Methods

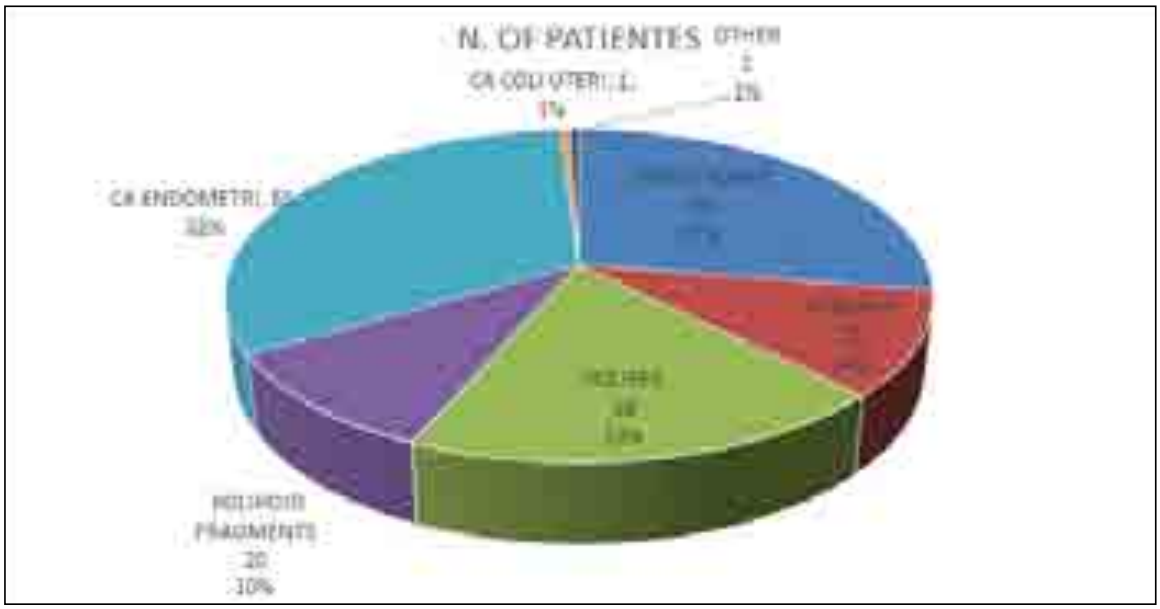
Our study is a retrospective study. Data for our study were collected from clinical gynecological charts in the university «Queen Geraldina».Object of our study were charts of 200 patients with diagnosis of postmenopausal bleeding from 1 January 2018- 31 December 2018. To provide more data we have called patients by telephone.

## Statistical analysis

IBM SPSS Statistics 25 test, Anova test, Spearman's Rho and Independent Samples test were for processing these data

## The results of the study

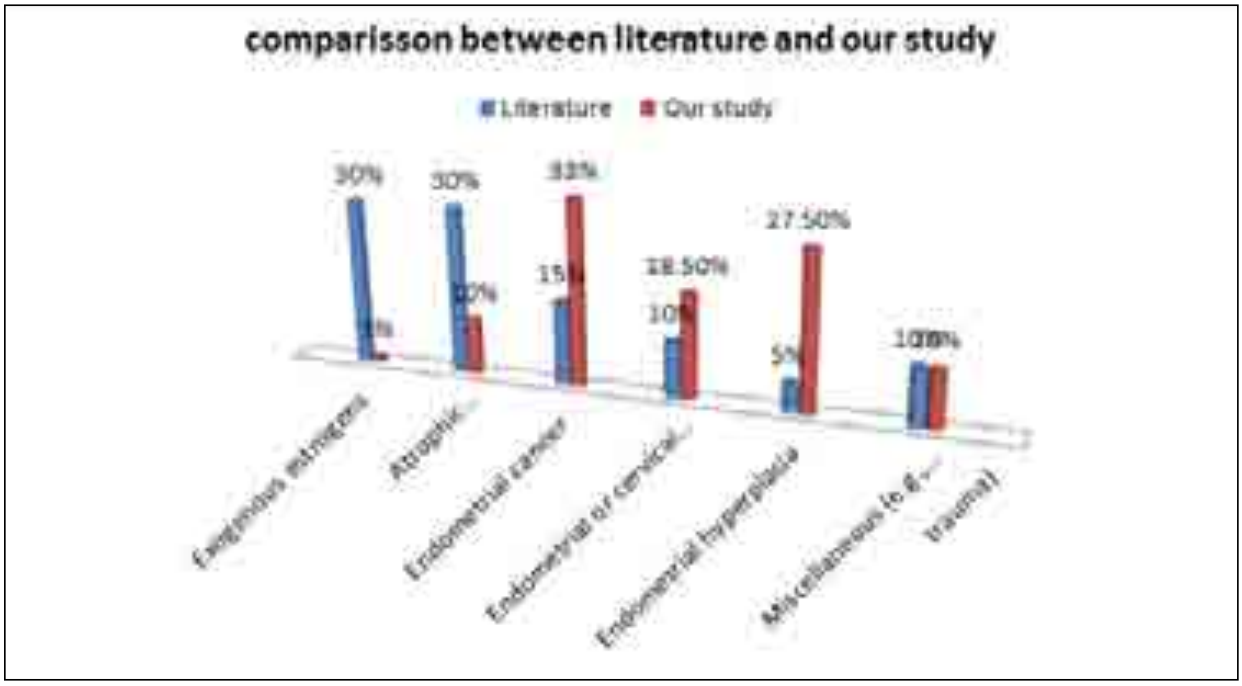
Among 200 clinical gynecological charts of the patients with the diagnosis of postmenopausal bleeding we found these results: 55(27.5 %) of them had Hypertrophy, 20(10%) had Atrophy;38(18.5%) had Polips;20(10%) polipoid Fragments;65(33%) had endometrial cancer;1(0.5%) had cervical cancer,1(0.5%) atipic squamous cells. This distribution of the cases of the postmenopausal bleeding is explained in the graph below.



As we can see from the graphic, endometrial cancer takes the first place with 33 %

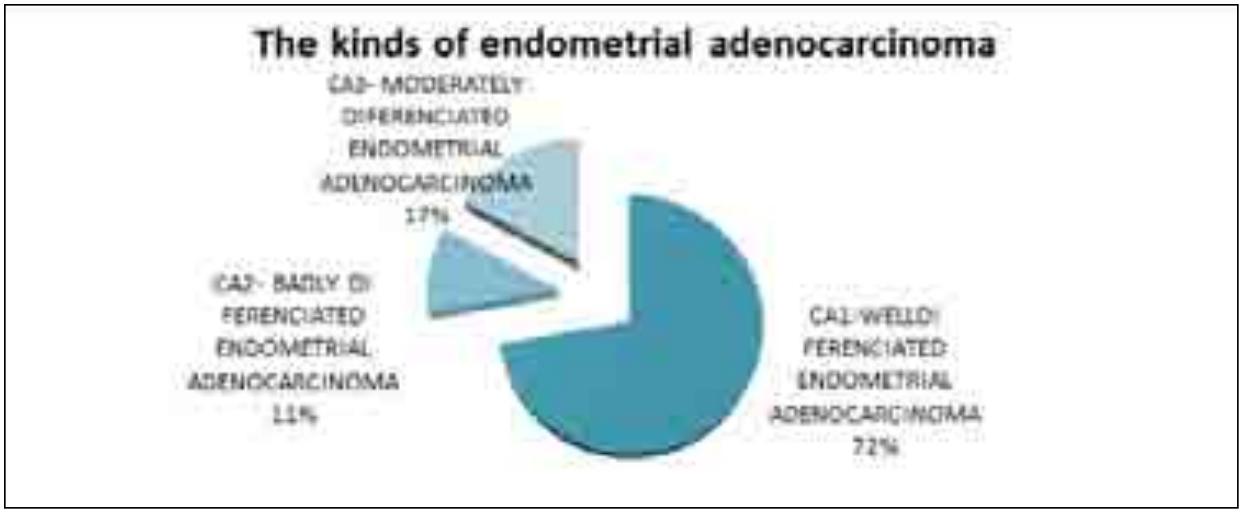
| FACTOR | Literature | Our study |
|---|---|---|
| Exogenous estrogens | 30 % | 1 % |
| Atrophic endometritis/vaginitis | 30 % | 10 % |
| Endometrial cancer | 15 % | 33 % |
| Endometrial or cervical polyps | 10 % | 18.5 % |
| Endometrial hyperplasia | 5 % | 27.5 % |
| Miscellaneous (e.g., cervical cancer, uterine sarcoma, urethral caruncle, trauma) | 10 % | 10 % |

Here we are comparing the results of literature studies and our studies. As we can clearly see in the graphic below endometrial cancer takes the first place in our study with 33 % but only 15 % in the studies of literature. The level of endometrial carcinoma in our study is two to three folds greater than in the literature causing a big problem. Exogenous estrogens take about 30 % in the literature but only 1% in our study making a big difference.




## *The kinds of endometrial adenocarcinoma*

| THE KINDS OF ENDOMETRIAL ADENOCARCINOMA | NUMBER (%) |
|---|---|
| CA1-WELL DIFFERENTIATED ENDOMETRIAL ADENOCARCINOMA | 47 (72.2%) |
| CA2- BADLY DIFFERENTIATED ENDOMETRIAL ADENOCARCINOMA | 7 (10.8%) |
| CA3- MODERATELY DIFFERENTIATED ENDOMETRIAL ADENOCARCINOMA | 11 (17%) |
| TOTAL | 65 (100%) |




We see that well differentiated endometrial adenocarcinoma in our study takes about 72 % of all endometrial carcinomas. These results are nearly the same with the results of the studies in the literature that accounts for about 80 %.

*Polips*

| Polips | Number of patients |
|---|---|
| Necrotized polip | 3 |
| Malign polip | 2 |
| Benign polipe | 32 |
| Polipoid fragments | 20 |
| Atipic polip | 1 |
| Total polips | 57 |

As we see, the polyps are generally benign in our study. The same thing happens in the studies of the literature. We found only two malign polyps.

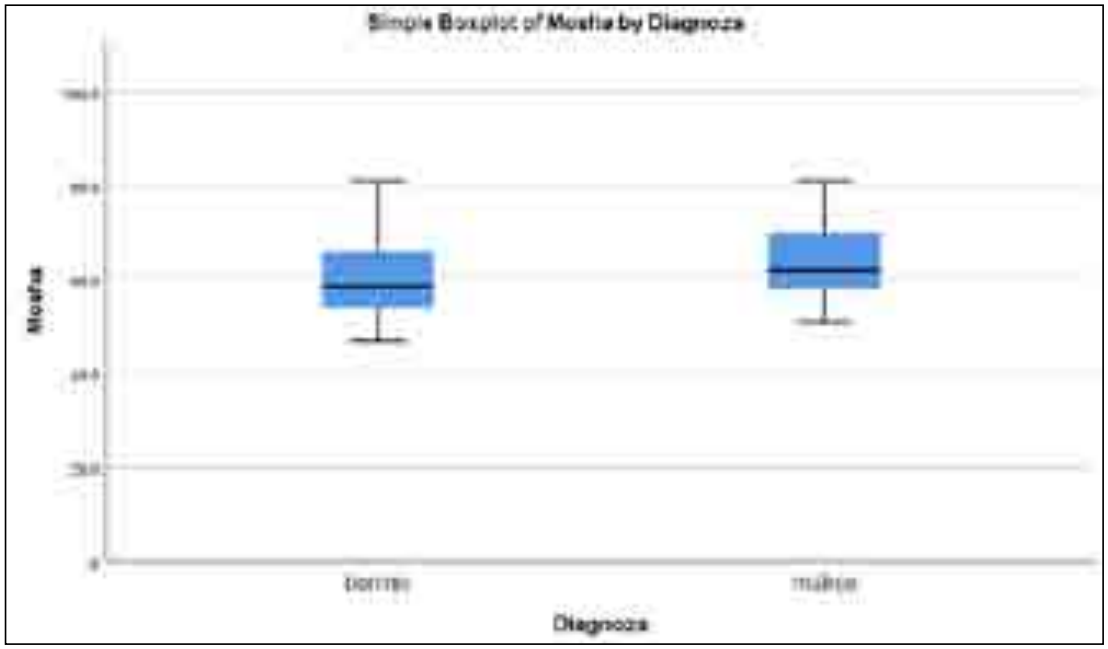
*65 Of patients diagnosed with endometrial cancer distributed by age*

| 65 OF PATIENTS DIAGNOSED WITH ENDOMETRIAL CANCER DISTRIBUTED BY AGE | |
|---|---|
| AGE | NR. OF PATIENTS |
| <50 | 1 |
| 50-55 | 6 |
| 55-60 | 17 |
| 60-65 | 13 |
| 65-70 | 14 |
| 70-75 | 5 |
| 75-80 | 7 |
| 80-85 | 3 |

We are calculating the correlation between diagnosis and age of the patients using Spearman's Rho statistical test. p= 0.032 ≤ 0.05

This p value tells us for a significant correlation between age and diagnosis. This tells us that with the increasing of the age of the patient, the likelihood of developing the endometrial cancer increases too.

| Correlations | | | | |
|---|---|---|---|---|
| | | | Diagnosis | Age |
| Spearman's rho | Diagnosis | Correlation Coefficient | 1.000 | .214* |
| | | Sig. (2-tailed) | . | 0.032 |
| | | N | 200 | 100 |
| | Age | Correlation Coefficient | .214* | 1.000 |
| | | Sig. (2-tailed) | .032 | . |
| | | N | 100 | 100 |
| *. Correlation is significant at the 0.05 level (2-tailed). | | | | |



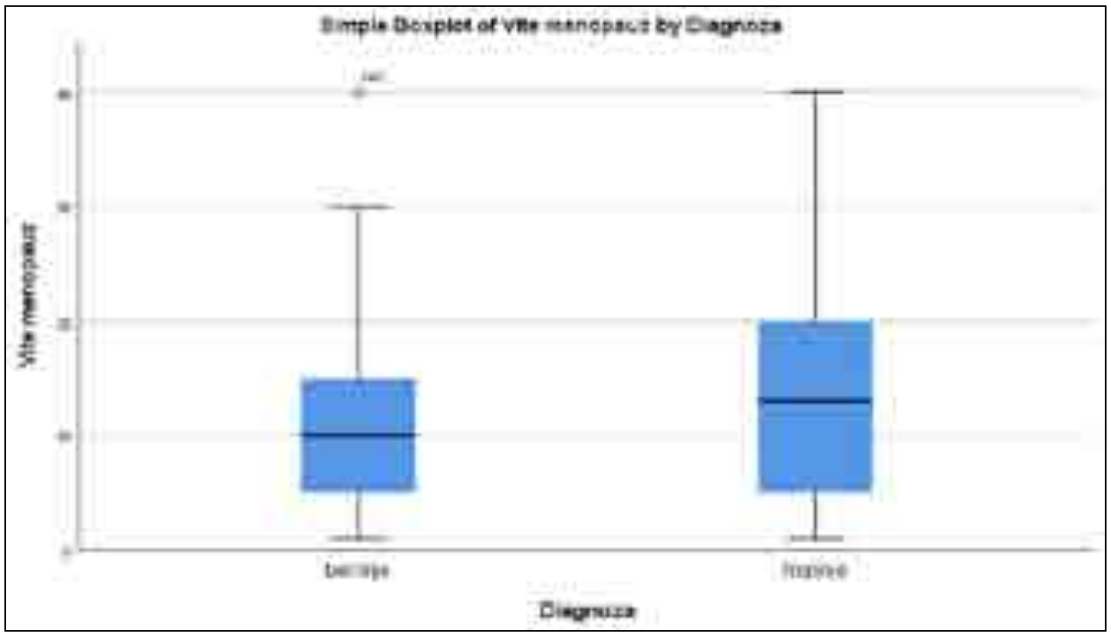

*Here is the correlation between the diagnoses and years in menopause.*

| Years in menopause | polip | atrophy | endometrium cancer | hypertrophy |
|---|---|---|---|---|
| <5 vjet | 3(3%) | 2(2%) | 5(5%) | 7(7%) |
| 5-10 vjet | 3(3%) | 2(2%) | 10(10%) | 9(9%) |
| 10-15 vjet | 2(2%) | 4(4%) | 4((4%) | 9(9%) |
| ≥15 vjet | 8(8 %) | 4(4%) | 12 (12%) | 10(10%) |

We are calculating the correlation between diagnosis and age of the patients using Spearman's Rho statistical test. p= 0.028 ≤ 0.05.

This p value tells us for a significant correlation between years in menopause and diagnosis. This tells us that with the increasing of the years in menopause of the patient, the likelihood of developing the endometrial cancer increases too.

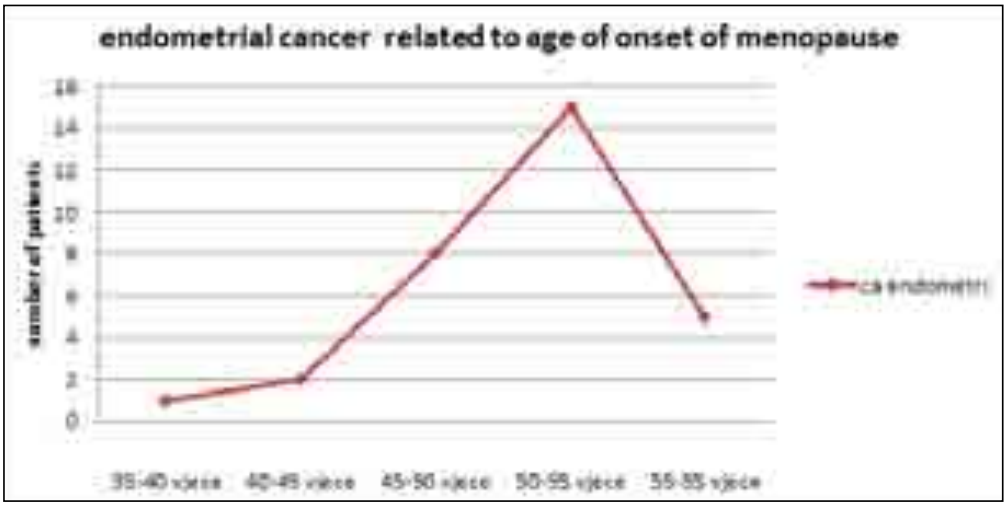
| | | | Diagnosis | Years in menopause |
|---|---|---|---|---|
| Spearman's rho | Diagnosis | Correlation Coefficient | 1.000 | .113 |
| | | Sig. (2-tailed) | . | p=0.028 |
| | | N | 200 | 165 |
| | Years in menopause | Correlation Coefficient | .113 | 1.000 |
| | | Sig. (2-tailed) | .148 | . |
| | | N | 165 | 165 |




*In the table below we have presented the distribution of diagnoses depending on the age of the onset of menopause.*

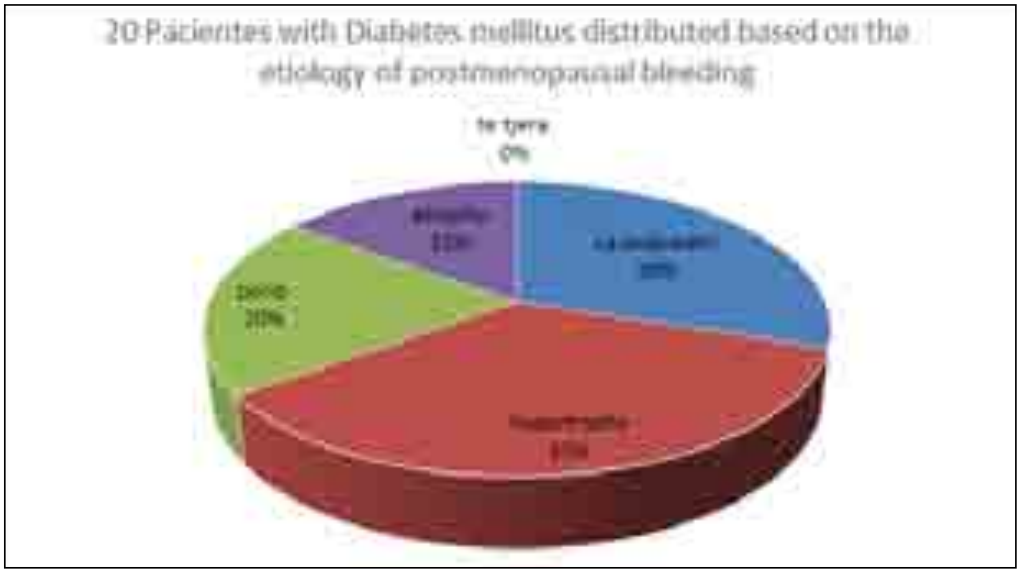
| Age of onset of the menopause | polip | hypertrophy | Endometrial cancer | atrophy |
|---|---|---|---|---|
| 35-40 | 0 | 2 | 1 | 1 |
| 40-45 | 2 | 4 | 2 | 2 |
| 45-50 | 4 | 12 | 8 | 1 |
| 50-55 | 7 | 12 | 15 | 7 |
| 55-60 | 3 | 5 | 5 | 1 |

We can see that endometrial cancer is more often in the age of onset of menopause 50-55 years of age.




*In the table below, we have distributed the patients with diagnoses that cause postmenopausal bleeding in two group, these who have diabetes and those who have not.*

| paciente me, | kane diabet | nuk kane diabet | total |
|---|---|---|---|
| ca endometri | 6 | 25 | 31 |
| hipertrofi | 7 | 18 | 25 |
| polipe | 4 | 14 | 18 |
| atrofi | 3 | 9 | 12 |
| te tjera | 0 | 14 | 14 |
| total | 20 | 80 | 100 |

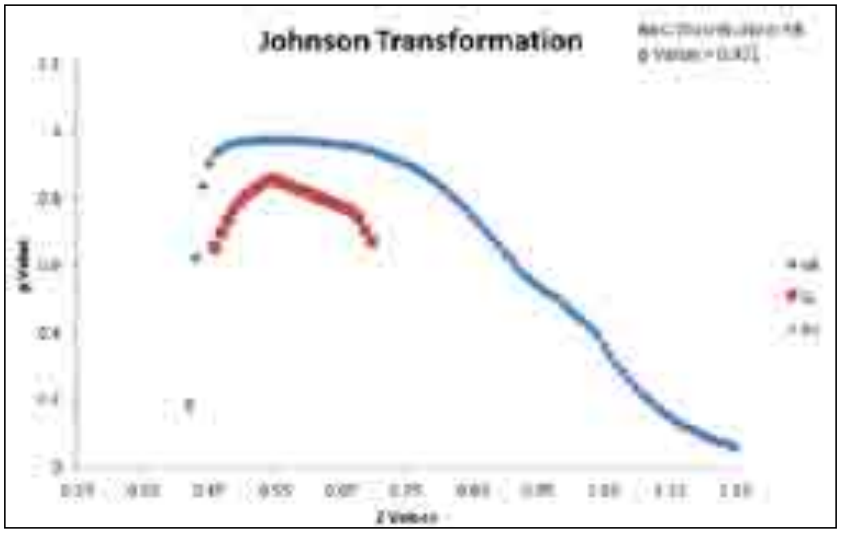


We are calculating the correlation between endometrial cancer and Diabetes mellitus of the patients using Anova statistical test. p= 0.632 ≥ 0.05

This p value tells us for a non-significant correlation between the endometrial cancer and Diabetes mellitus. This tells us that Diabetes mellitus doesn't increase the likelihood of developing the endometrial cancer increases.

| Johnson Transformation Program | | | | | | |
|---|---|---|---|---|---|---|
| | Mean | StDev | Median | Min | Max | p Value |
| Original data | 10.00 | 7.688 | 8.000 | 0.000 | 25.00 | 0.632 |
| Transformed data | -0.0111 | 0.964 | -0.111 | -1.650 | 1.650 | 0.971 |

We recalculated the correlation between endometrial cancer and Diabetes mellitus of the patients Johnson Transformation Program using .p= 0.971 ≥ 0.05 This p value tells us for a non-significant correlation between the endometrial cancer and Diabetes mellitus. This tells us that Diabetes mellitus doesn't increase the likelihood of developing the endometrial cancer increases .




*Here is the table that shows the distribution of the patients with diagnoses that cause postmenopausal bleeding in two group, these who have HTA and those who have not.*

| paciente me | kane HTA | nuk kane HTA | total |
|---|---|---|---|
| atrofi | 4 | 8 | 12 |
| ca endometri | 29 | 2 | 31 |
| hipertrofi | 21 | 14 | 35 |
| polip | 7 | 11 | 18 |
| te tjera | 1 | 3 | 4 |
| total | 62 | 38 | 100 |

To see if there are significant differences between benign /malign diagnostic groups and HTA present /not present was used Anova test. This table shows significant differences between group of patients that have HTA and endometrial carcinoma, $p$= 0.021<0.05.

*Anova*

| HTA | | | | | |
|---|---|---|---|---|---|
| | Sum of Squares | df | Mean Square | F | Sig. |
| Between Groups | 1.256 | 1 | 1.256 | 5.519 | $p$=0.021 |
| Within Groups | 22.304 | 98 | .228 | | |
| Total | 23.560 | 99 | | | |

We are calculating the correlation between endometrial cancer and HTA of the patients using Spearman's Rho statistical test. $p$= 0.021<0.05.

This p value tells us for a significant correlation between HTA and diagnosis. This tells us that with the presence of HTA of the patient, the likelihood of developing the endometrial cancer increases too.

*Correlation between diagnosis and hta*

| | | | Diagnoza | HTA |
|---|---|---|---|---|
| Spearman's rho | Diagnoza | Correlation Coefficient | 1.000 | .231* |
| | | Sig. (2-tailed) | . | p=0.021 |
| | | N | 100 | 100 |
| | HTA | Correlation Coefficient | .231* | 1.000 |
| | | Sig. (2-tailed) | .021 | . |
| | | N | 100 | 100 |

*Correlation Between Endometrial Cancer and Endometrial Thickness*

| Endometrial thickness | polip | ca endometri | hypertrophy | other |
|---|---|---|---|---|
| <5mm | 0 (0%) | 0(0%) | | 2(2.7%) |
| 5-10mm | 6(8.1%) | 3(4%) | 5(6.7) | |
| 10-15mm | 7(9.5%) | 4(5.4%) | 15(20.2%) | |
| >15 | 4(5.4%) | 7(9.5%) | 7(9.5%) | |
| irregular | 0(0%) | 14(19%) | | |
| TOTAL 74 PATIENTES | | | | |

We are calculating the correlation between the etiologies of the postmenopausal bleeding and endometrial thickness of the patients using Spearman's Rho statistical test. ***p***= 0.019<0.05.

This p value tells us for a significant correlation between etiologies of the postmenopausal bleeding and endometrial thickness. This tells us that with the increasing of endometrial thickness of the patient, the likelihood of developing the endometrial cancer increases too.

## *Correlation Between Endometrial Cancer and Endometrial Thickness*

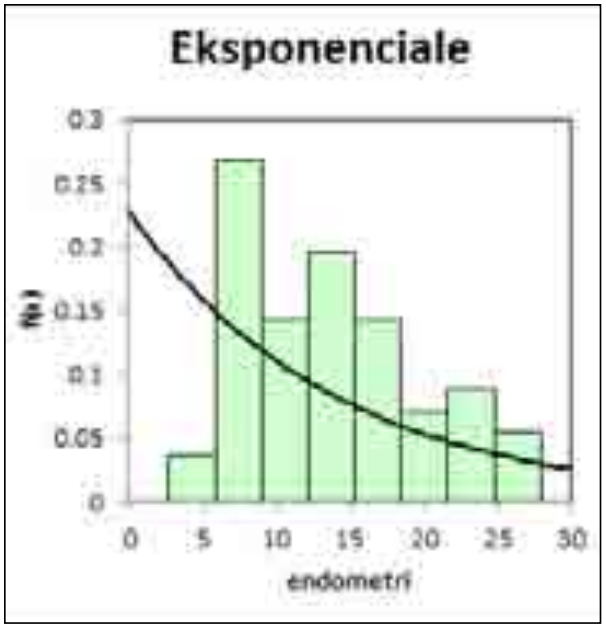
| | | | Diagnoza | Dimensionet |
|---|---|---|---|---|
| Spearman's rho | Diagnoza | Correlation Coefficient | 1.000 | .272* |
| | | Sig. (2-tailed) | . | 0.019 |
| | | N | 200 | 74 |
| | Dimensionet | Correlation Coefficient | .272* | 1.000 |
| | | Sig. (2-tailed) | .019 | . |
| | | N | 74 | 74 |

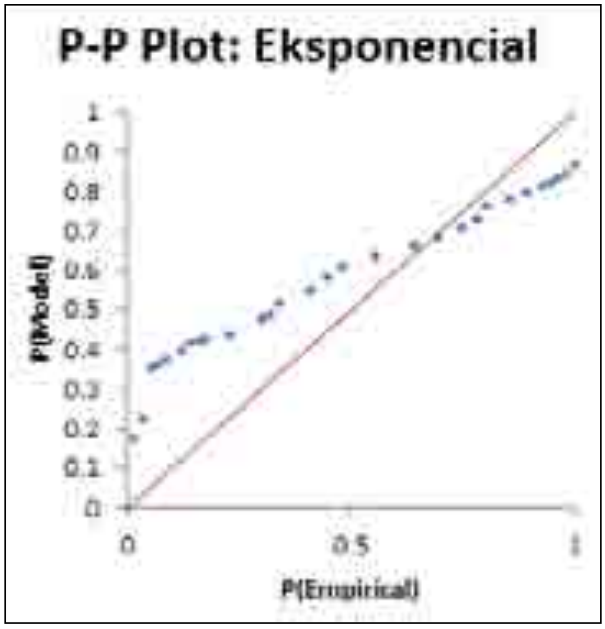
*Correlation is significant at the 0.05 level (2-tailed).

We are calculating the correlation between the endometrial cancer and endometrial thickness .***p***= 0.001<0.05.This p value tells us for a significant correlation between endometrial cancer and endometrial thickness.

## *Results of Eksponencial distribution*

| Count | Mean | StDev | Median | Min | Max | Skew |
|---|---|---|---|---|---|---|
| 56 | 13.88 | 6.092 | 14.00 | 2.700 | 28.00 | 0.384 |
| Location | Shape | Scale | Threshold | Log-Likelihood | AD | p Value |
| | | 13.88 | | -203.3 | 7.926 | <0.001 |




This graphic shows us that with the increasing of endometrial thickness of the patient, the likelihood of developing the endometrial cancer increases too.

## *Correlation between weight and endometrial cancer*

| Weight | N.of Patients with Hypertrophy | N. of Patients with Endometrial Ca |
|---|---|---|
| Normal Weight | 6(17%) | 6(19%) |
| Overweight | 29(83%) | 25(81%) |

We looked for a correlation between weight and endometrial cancer, was used Spearman's rho test but no important correlation was found, , p=0.855 >>> 0.05.So overweight doesn't influence development of endometrial cancer.

| | | | Pesha | Diagnoza |
|---|---|---|---|---|
| Spearman's rho | weight | Correlation Coefficient | 1.000 | -.019 |
| | | Sig. (2-tailed) | . | .855 |
| | | N | 100 | 99 |
| | Diagnoses | Correlation Coefficient | -.019 | 1.000 |
| | | Sig. (2-tailed) | 0.855 | . |
| | | N | 99 | 99 |

To put the diagnosis of postmenopausal bleeding is used pelvic examination, transvaginal ultrasonography, hysteroscopy, dilatation and curettage.

Treatment was hysterectomy in endometrial carcinoma, malign polyp, cervical cancer, polipectomia in the cases of benign polyps.

## Discussion

It is very important to discuss the results of endometrial cancer in our study because we found the level of endometrial cancer very high, taking the first place 33 % in comparison with other causes of posmenopausal bleeding. In comparison with the percentage of endometrial cancer of the studies of the literature , the value of our study is two to three fold greater than that of literature. These results disturbed us and we must try to find an explanation to our results.

We think that gynecologist in other cities and in private clinics treat all benign cases of postmenopausal bleeding but they refer difficult cases like endometrial cancer in our university hospital, so increasing the cases of endometrial cancer and so the percentage in our study, reducing the percentage of benign cases.

Another point is that usage of egzogene estrogens in the studies of literature is 30 % but in our study only 1 %.This can happen because our patient are frightened to use them because of negative effects. This is another factor that decreases the percentage of benign causes of posmenopausal bleeding, and allows the malign factor to take the first place.

## Conclusions

In our study the causes of postmenopausal bleeding are;

1. endometrial cancer
2. hypertrophy
3. atrophy
4. polips
5. others

Endometrial cancer is in a high level, taking the first place with 33 %.

Age, menopausal age, years in menopause, endometrial thickness, HTA have a significant correlation with endometrial cancer. So we can say that these factors increase the likelihood of developing of endometrial cancer.

In our study we found no significant correlation between diabetes, obesity and endometrial cancer. So the results of our study show that diabetes and obesity don't increase the likelihood to develop endometrial cancer.

## Recommendation

We recommend a large prospective study to verify the percentage of endometrial cancer in Albania and to look for other factors that can contribute in the development of endometrial cancer.

## Referenca

**1. BEREK &NOVAK GYNECOLOGY** (Sixteen Edition)
**2. FIGO** (International Federation Of Gynecology And Obstetrics)
**3. ACOG** (The American College Of Obstetricians And Gynecologists)

# *Mycosis Fungoides. Differencial Diagnosis*

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## Abstract

***Background:*** *Mycosis funguides (MF) is a rare malignant skin neoplasms, and one of the most common primary cutaneous T cell lymphomas. MF have the appearance of many skin lesions, particularly in its early clinical course, creating diagnostic challenges, especially in our country ( growing countries) as it requires tissue biopsy, histological diagnosis with hematoxylin & eosin, immunohistochemistry and molecular diagnostic elements.*

***Materials and Methods:*** *This is a differencial diagnosis based on retro and pro spective study, about 6638 articles published in Pubmed for Cutaneous Lymphoma (CL ) with focus MF,33 articles of Primary Cutaneous CD 30+,WHO-EORTC classification for CL and recently updated articles about MF. All these evidence of the MF were reviewed and analyzed.*

***Results:*** *In this study was reviewed, the importance of bioptic examination for the diagnosis of MF and other examinations such as immunohistochemistry, and the histopathological finding of MF were again reviewed and definied. And it was given a panel of the differential diagnosis of this pathology that mimics many inflammatory pathologies in particular Spongiform Dermatitis, and neoplasmic skin lesions like Sezary Syndrome and Primary Cutaneous CD 30+- T cell Lymphoma, to warn clinicians of the wide spectrum of this difficult disease.*

***Conclusion:*** *The classification of cutaneous lymphomas is multidisciplinary and needs the correlation between clinical, histopathological, immunohistochemical, and molecular diagnostic elements. It is important to be suspected of MF when an erythematosus process has long-lasting progression, poor responses to medications for other inflammatory pathologies, and most importantly during histopathological examination to detect atypical lymphocytes in the epidermis.*

***Key words:*** *Mycosis fungoides, differencial diagnosis,Primary Cutaneous Lymphoma, inflammatory skin diseases*

## Introduction

Primary cutaneous lymphomas are classified in the group of extranodal non-Hodgkin Lymphomas.

Primary cutaneous lymphomas have a different clinical attitude and prognosis from systemic lymphomas involving the skin secondly, and for this reason require different types of therapies.

Hence, recent classification systems such as the EORTC classification for primary cutaneous lymphomas and the WHO classification for tumours of haematopoieticand lymphoid tissues considered primary cutaneous lymphomas as separate entities.

They may be: T cell, B cell, or NK cell origin.[6,7]

Cutaneous T Cell lymphomas (CTCL) include a group of lymphomas in which:*Mycosis fungoides* is the most primary, common type of CTCL.

It is a cutaneous lymphoma that originates in the memory T-cells (CD45RO+), which express the T-cell receptor (TCR) and CD4+ immunophenotype.[1]

**The etiology** and risk factors of the disease are unclear.

**Clinical Variants** are (as report in the WHO-EORTC Classification for Cutaneous Lymphomas)

- Follicular or folliculotropic mycosis fungoides
- Pagetoidreticulosis or Woringer- Kolopp type
- Granulomatous slack skin[6,7]

**Histopathology** of mycosis fungoides varies in stages of the disease.

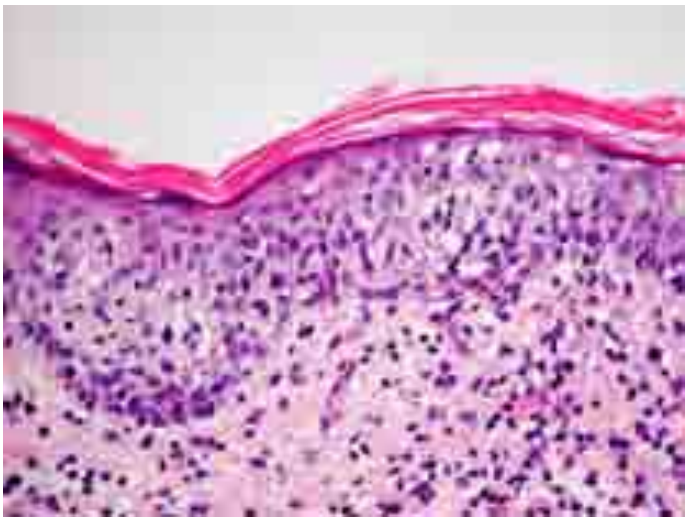
Epidermal lymphoid infiltrate, (epidermotropism) with absent or rare spongiosis, and lymphoid atypia (cerebriformcells, which are the diagnostic cells) are the main features.

*Patch stage*

The histological diagnosis of MF in its early stages is difficult, as the disease resemble as an inflammatory skin diseases

Patchy lichenoid infiltrate of lymphocytes in thickened papillary dermis and in small collection within a minimally spongiotic epidermis (Atypical lymphocytes cerebriform cell circumscribed to the epidermis (epidermotropism)).

Epidermis may show psoriasisform hyperplasia



*Plaque stage*

Findings are similar to those seen in patch stage, but the infiltrate is denser.

The epidermotropism is more noticeable and the presence of intraepidermal collections of atypical cells (Pautriermicroabscesses) is a real feature close to diagnose. Lymphocytes may be cytologically atypical.

*Tumor stage*

In this stage the epidermotropism is lost and the tumor cells ( atypical lymphocytes) increase in number and size.In this part of the disease are present medium to large lymphoid cell (blast cells with large nuclei and prominent nucleoli)[1,2]

*Immunohistochemistry*

Tumour cells have a mature CD3+, CD4+, CD45RO+ memory T-cell phenotype. In same cases is documented a CD4– /CD8+ mature T-cell phenotype (MF, cytotoxic immunophenotype variant). Similar cases have the same clinical feature and prognosis as CD4+ cases. With the progression of the disease loss of CD2, CD5, and CD7 may be seen. When large blast stage take place, cells can express the CD30 molecule and/or a cytotoxic phenotype.[2,5] *An image of MF in early stage..*[22]

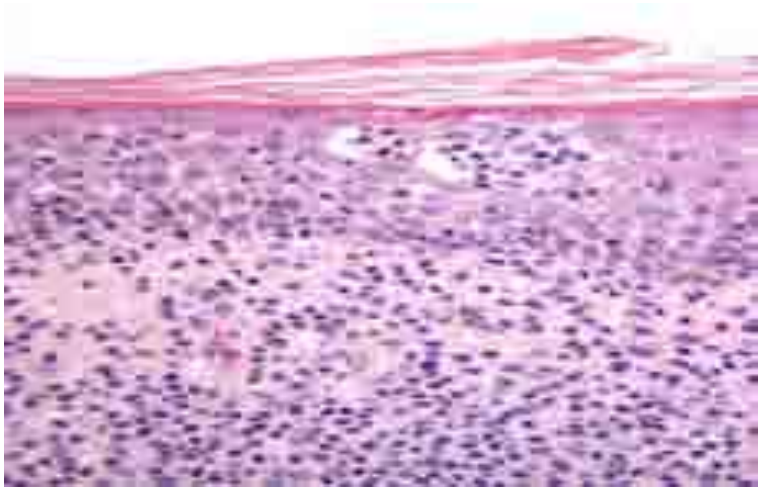


Image of Pautrier microabcesses

*Primary cutaneous CD30+ T-cell lymphoproliferative diseases are the second most common category of CTCLs.* CD30-positive CTCLs include: lymphomatoidpapulosis (LP), anaplastic large cell lymphoma (ALCL), and some cases of mycosis fungoides with large cell transformation (MFLCT).[7] *Images og plaque-stage, when are seen the Pautrier microabcesses*[22]

## Materials and Methods

This is a concentric, factual, and descriptive retro- and prospective analysis of MF. Our study is supported in detailed review of more articles about MF, published in

Pubmed, or Free article and our little experience in diagnosis this entity through clinical, histopathological, immunohistochemical elements.

Some of these articles are updated lately.

In practice, the diagnosis of MF in an early stage can be very challenging because clinicopathologic features overlap with various inflammatory dermatitis and conflict with clinical presentations and pathologic features.[10]

## Results

### *Inflammatory process, not mycosis fungoides*
### *Explanation*

Different histopathologic findings are nearly related to skin diseases, more than 40 different benign dermatitis – most of them inflammatory dermatoses such as eczema, psoriasis, nonspecific dermatitis, lichen, lupus, pseudolymphoma, parapsoriasis, and toxidermia have been interpreted as being clinically and pathologic imitated by mycosis fungoides.

In the first place need to be specified the histological data about MF. [11,13]

Many studies confirmed that the characteristic histopathologic features of MF in **an early stage** include enlarged epidermal lymphocytes with cerebriform nuclei in the epidermis and epidermotropism, and others features which are mention above.Despite this, none of these features are entirely specific for MF.After all the pattern may vary, epidermotropism is considered an emblem of MF.

Pautrier microabsces are atypical lymphocytes tend to become aggregation in round collections in the epidermis, named

wrong for Pautrier (it was Darier who described them first) is considered more specific for MF but is only seen in a few lesions.A variety of inflammatory and neoplastic diseases may look-alike MF if only changes in the epidermis alone are taken into account.[14]During histopatological examination, the doctor see neutrophils in the dermis or in the epidermis, extravasation in number of erythrocytes in the papillary dermis and sometimes in the epidermis, marked spongiosis and/or ballooning of the epidermis, and mounds of parakeratosis staggered between zones of orthokeratosis in a cornified layer.[9,12] When one or more of the signs are presented, an supposition justified that the process is inflammatory and evolving, and not neoplastic.

However, an epidermis that have changes that look closely those of mycosis fungoides and edema is prominent in the papillary dermis, a pathologist can conclude, perfectly, that the disease is not mycosis fungoides, but an inflammatory one.[9,12]

According to Differencial Diagnosis in Surgical Pathology ‘s book Spongiotic Dermatitis is one of the most closely related disease, that have the same findings as MF in an early stage.[3]

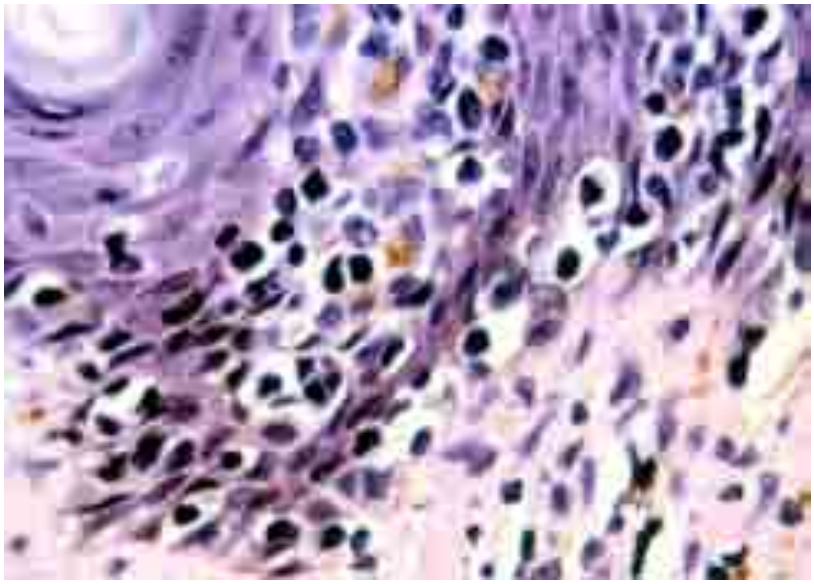
The difficulty arises because collections of mononuclear cells are present in discrete foci in the epidermis of both conditions.

But, when a histopathologist sees no pure population of lymphocytes, numerous cells that have prominent stellate cytoplasm ( keratocytes )mixed with Langerhans cell,there is no doubt for a manifestation of spongiotic dermatitis.

Also we mention the importance of Pautrier ‘ s collections.

The red blood cells tend to be extravasated in the upper part of the dermis of some spongioticdermatitides, but none in mycosis fungoides.

In short, the findings in mycosis fungoides are the antagonistic of those in spongioticdermatitides.[11]



An image of a Halo Lymphocites [22]

## Sezary ‘s sindrom vs mycosis fungoides

### *Explanation*

Sezary’s Sindrom (SS) is a variant of Mycosis Fungoides represent an erythrodermic form of it with neoplastic cells (Sezary cells ) populating the peripheral blood.

The characteristics between those pathologies are very difficult. The histopathologicalfinding and the immunostaining are exactly like MF.[16]The immunohistochemical pattern of Sezary syndrome is CD3+, CD4+, CD7-, and CD8- cells,same as MF.To differentiate those pathologies is used immunostaining

for MUM-1 (multiple myeloma oncogene) because it is positive in Sezary syndrome and negative in mycosis fungoides.

MF and SS may be distinguished by identification of certain molecules, including Programmed-Death-1.[15]

## Primary cutaneus cd30+ t-cell lymphomas vs mycosis fungoides

### *Explanation*

As MF progresses **to the tumor stage**, the infiltration of atypical lymphocytes shares a nodular pattern in the dermis with loss of epidermotropism, and others situations( the formation of a large atypical lymphocytes –the blasts) mention above in tumor stage. The important thing during this phase is the expression of the atypical lymphocytesof CD30 molecule, complicating the differential diagnosis with others limphoproliferativ disorders like Primary Cutaneus CD30+ TcellLymphoma.It is needed to point out, even in this case when MF express CD 30+, that the definitive diagnosis of MFLCT requires the clinical history(clinical assessment) and cutaneous infiltration by large atypical lymphocytes.[17] The difference diagnosis is made between MF and CD30-positive CTCLs include: lymphomatoidpapulosis (LP), anaplastic large cell lymphoma (ALCL).

LP is classified as a low-grade CTCL, in the spectrum of cutaneous CD30-positive lymphoproliferative disorders.[3,20]Histopathologically, LP can present itself in four different patterns type A,B,C and D.

LP type B is characterized by small to medium CD4-positive lymphocytes and are often CD30-negative, with cerebriform nuclei with epidermotropism. These findings are identical as in MF. [1,18]

But, the definitive diagnosis of LP requires close clinical-pathological correlation, especially when it comes to the last common histologic subtypes (B, C, and D).[20]

ALCL is a CD30-positive non-Hodgkin's lymphoma, classified by the World Health Organization .

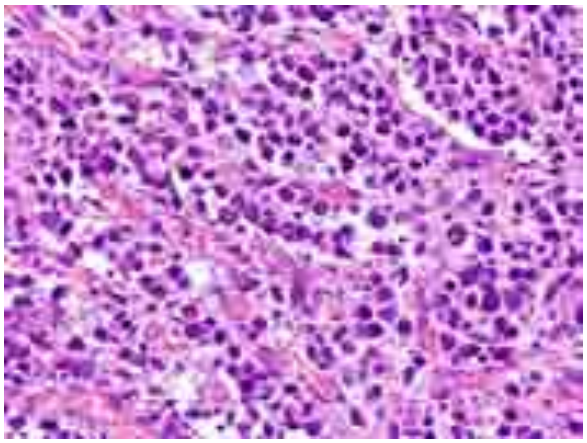
Microcsopically ALCLs shows evidence of diffuse dermal infiltrate of lymphoid cells containing large, round, oval, or irregular vesicular nuclei, with prominent and eosinophilic nucleoli and abundant cytoplasm. The epidermotropism is absent.

The large lymphoid cells show strong positivity for CD 30+ molecule in the form of diffuse membrane staining, as well as a paranuclear dot-like reaction in the Golgi area.[19]

According to genetic level, this tumor is characterized by the chromosomal translocation t(2;5), which generates the chimeric NPM-ALK transcript.

This can be detected by immunohistochemistry, RT-PCR and in situ hybridization in the lesional tissue.

In contrast of systemic CD30+ lymphomas, most C-ALCs express the cutaneous lymphocyte antigen (CLA), but do not express the epithelial membrane antigen (EMA) and the anaplastic lymphoma kinase (ALK; indicative of the t2;5 chromosomal translocation or its variants).[21]



Anaplastic large cell lymphoma

-CD30 positive,diffuse, uniform staining in all tumor cells (membrane and Golgi zone pattern)[22]

## Conclusion

Mycosis fungoides is the most frequent primary cutaneous lymphoma and various differential diagnoses can be made especially in the early phases of the disease. Sometimes it can be difficult to suspect and diagnose from the clinical presentation to histopathological and immunohistochemical findings. Hence it requires good knowledge of the disease from both clinicians and pathologists.

The aim of this article is to highlight the importance of close clinico-pathological correlation for an accurate diagnosis.

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# *Stroke and Atrial Fibrillation in Dialysis Population*

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## Abstract

***Introduction:*** *The dialysis population have a risk 5-10 fold higher for developing cardiovascular disease than age matched controls. Patients in dialysis have a risk for stroke 10 time more then the general population. Cardio-embolic stroke in dialysis population count a high percentage perhaps of the increased prevalence of atrial fibrillation.*

***Methods:*** *A search in the literature for different study who combined AF with chronic Kidney disease, dialysis and stroke. We compare it with our findings in a retrospective study from November 2008 to December 2019 which included 1732 patients. From analyzed data, 70 patients experienced a cerebrovascular event during this period. we compared data with a control group of 70 patients without stroke.*

***Results:*** *In our study 1732 patients who was treated in American Hospital during November 2008-december 2019 were observed. 70 patients had a cerebro-vascular*

*accident (CVA). In 16 patients who experienced CVA, AF was present. In the control group AF was present in 7 patients.*

***Discussion:*** *In different study the presence of AF at baseline it's more associated with a high mortality but there are no clear evidence of association between the presence of AF and stroke. The presence of AF represents a marker of comorbidity and advanced age rather then a cause of mortality. Its possible that hemodialysis –related AF may carry a lower risk of stroke than AF in general population.*

***Key words:*** *atrial fibrillation, hemodialysis, stroke*

## Introduction

For every 10 ml/min/1.73 m 2 reduction in glomerular filtration rate (GFR), the risk of stroke increases by 7% (11). For this reason Chronic Kidney Disease (CKD ) staging may also be a useful clinical tool for identifying people who may benefit most form interventions to reduce cardiovascular risk. (11) Patients on hemodialysis carries up a risk for stroke 10 time higher than those with normal function.(6). The risk factor for CVA in hemodialysis may differ when compared to the general population. Patients on dialysis and End stage Renal Disease, (ESRD) are at 5-10 fold higher risk for developing cardiovascular disease(CVD) than age matched controls(15). Clinically , CVD in this population manifests as coronary artery disease, arrhythmias, stroke or congestive heart failure. Beyond the traditional risk factors (Diabetes Mellitus and hypertension) uremia-specific factors that arise from accumulating toxins also contribute to the pathogenesis of CVD(15). Stroke risk in dialysis patients appears to be greater than that for CAD. The risk of stroke in ESRD is 5-10 time higher than general population (6). Whereas the relative risk of myocardial infarction in ESRD is 2.5-3 fold (16-7)

Risk appears to be proportionally increased for both ischemic and hemorrhagic strokes (7).Causes of hemorrhagic stroke may differ from ischemic stroke in patients in long term dialysis therapy and thus acquired risk factors could account for this later hemorrhagic stroke risk (7). Reason could include excess vascular calcification and stiffness,(18-19) leading to worsening hypertension. This combined with the use of anticoagulation on dialysis therapy, could increase hemorrhagic stroke (13)

Cardio-embolic strokes account for a relatively large proportion of ischemic strokes within the dialysis population (7), perhaps because of the increased prevalence of atrial fibrillation (15) . Cardio-embolic risk factors , in the CHOICE study, such as arrhythmias, left ventricular hypertrophy, valvular disease, and congestive heart failure, were not significantly different between individuals who experienced a cerebrovascular event versus those who did not , suggesting that

these aspects may not be correctly identified in dialysis patients (7). Measurement of cardiac function by echo-cardiography, chest radiography and physical examination is suggested for all patients before initiating hemodialysis therapy.

Having CKD/ESRD is associated with an increased prevalence of AF and vice versa (20) . The prevalence of AF in patients with advanced CKD has been reported 4-21% and in dialysis patients 7-27 % (20). The presence of AF confers a high risk of stroke in patients with CKD and ESRD. (20).

Different studies have reported the incidence of AF in ESRD patients varying from 1.0 to 14.8 per 100 person-years (26-28-29) Goldstein et a (29) reported an AF incidence of 148/1000 person-years in a Medicare database with a total of 258,605 elderly ESRD patients. Wizemann et a (30) using the data from international Dialysis Outcomes and Practice Patterns Study to analyzed the incidence, prevalence, and outcomes of AF among HD patients. Age, gender, racial, and geographical factors might considerably influence the incidence of AF among different population studies

The decision to anticoagulate patients with AF and ESRD is much more controversial given the associated increased bleeding risk (21). Patients on hemodialysis are at particularly high risk of suffering a serious bleed, which may outweigh any stroke risk reduction conferred by anticoagulation (22). Furthermore, the risk for vascular calcification may be enhanced by warfarin use (21).

There are two different opinions on the use of anticoagulation in AF patients on dialysis: -is safe and beneficial the use (23) and the other that the risks are not justified given the poorly benefits that are documented (24). The second opinion is the one predominating

All the currently available non-vitamin-K-oral anticoagulation's have a degree of renal excretion, and all trials have excluded patients with advanced CKD (21). So this agents should be used as they were studied in their respective trials and should not be used in patients with advanced CKD (estimated GFR<30 ml/min/1.73m2) (25).

There have also been reports of worsening renal function in patients with CKD treated with aspirin (31).

As for the anticoagulation in AF , the decision to treat with antiplatelet agents to prevent ischemic stroke is probably best individualized.

## Methods/ Results

We conducted a retrospective, qualitative and descriptive study which involved 1732 patients treated frequently 3 times a week in 5 hemodialysis centers in American Hospital during November 2008 to December 2019. From the analyzed

data 70 patients experienced a cerebro-vascular accident during this period of time. We compared the data with a control group of 70 patients, from this population, without a stroke event.

## Discussions

There is evidence that there is no increased rate of stroke in patient with AF when compared with non AF on survival analysis (14). The presence of AF at baseline its more associated with a high mortality but there are no clear evidence of association between the presence of AF and stroke (14) the presence of AF represents a marker of comorbidity and advanced age rather than a cause of mortality (14). Hemodialysis favors the AF through rapid shifts in fluid and electrolytes (potassium), and episodes of AF are common during dialysis . Although hemodialysis-induced AF may contribute to the increase in stroke risk in those initiating dialysis, it must be acknowledged that patients are anticoagulated during their dialysis sessions. It is possible that hemodialysis – related AF may carry a lower risk of stroke than AF in general population.

With the recent emergence of novel oral anticoagulants, there is an urgent need for a better understanding of the complex inter-relationship among CKD, atrial fibrillation, stroke, and bleeding risk. This knowledge is paramount to optimize the potential benefits of treatment and minimize the potential harms in this very high-risk and growing population (21)

In our study we found that AF was present in 16 patient from the 70 patients who experienced stroke events. In the control group AF was present in 7 patients. The mean age of the stroke group was 57.6 years. AF in our stroke group its related with comorbidity and age. In the control group the mean age is 53.69 years and AF was presented in 7 patients.

The risk of stroke declined by 2 months after initiation of dialysis, then fluctuated and gradually stabilized at approximately twice the baseline rate 1 year after initiation (10)

Although AF has little to no impact on the risk of stroke in patients on dialysis, AF is associated with adverse events (26). AF is associated with all-cause mortality (hazard ratio, 1.32-1.82) and cardiovascular events (hazard ratio, 1.39-2.15) in patients on dialysis (26). Interestingly, in a study on this issue, the incidence of non-cardiovascular death has seemed higher in patients with AF (103.0 per 1,000 patient years) than in those without AF (37.9 per 1,000 patient years), although AF was found to not be associated with the risk of non-cardiovascular death in another study (26-27). The presence of AF may indicate a poor prognosis in patients on dialysis (26).

Clinical diagnosis of AF is largely based on electrocardiogram, so we believed our study could represent most of the AF population. Finally, our study lacked specific data on dialysis vintage, fluid management during dialysis sessions, and intradialytic hemodynamic change, and we did not analyzed specific medications which might influence AF in this population.

In conclusion, increased risk of AF is noted among ESRD patients on dialysis especially with certain comorbidities. Although we can only show a relationship, not causality, between dialysis and incident AF, this relationship is clinically crucial since it can help physicians to pay more attention on AF related morbidity and mortality among dialysis patients.

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# *The new Coronavirus diseases (COVID-2019): A global Public Health Emergency*

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**Abstract**

*Public health is facing threats from diseases that are periodically emerging, many with the potential to cause pandemic with social and economic impact worldwide. World Health Organization (WHO) in 2015, has compiled a list of top diseases with potential to generate a public health emergency, and need urgent attention. According to WHO, the list will be reviewed annually or when new diseases emerge. WHO has compiled a list of top 10 threats to global health to focus in 2019. The list contains a number of serious issues but emerging infectious diseases dominate WHO's list. On 31 December 2019, WHO was informed of cases of pneumonia detected in Wuhan City, China which identified as a novel (new) type of coronavirus that has not been previously identified in humans. WHO has confirmed COVID-19 (a shortened version of coronavirus disease 2019) as the name of the disease that CoV infection causes. Coronaviruses are a zoonotic viruses that cause illness from the common cold to more severe diseases such as MERS&SARS. The situation of Covid-19 is rapidly evolving with case counts and deaths increasing each day. On January 30, WHO announced that COVID-19, was a public health emergency of international concern, as latest figures show that 9,826 people have been infected and 213 have died and rates the global risk assessment as high. Cases have been reported and in 26 countries outside of China. On February 20, globally 75 748 cases are confirmed, and 2121 deaths. WHO is working with researchers and other experts to coordinate global work to provide advice and to support countries to prevent the spread of this current*

*outbreak. Countries have shared information with WHO under the International Health Regulations -IHR 2005, to prevent, protect, control and provide a public health response to the international spread of disease.*

***Key words:*** *Emerging diseases, coronavirus, covid-19*

## Introduction

Public health is facing threats from emerging diseases due to the evolution / adaptation of microbes and the re-emergence of old diseases due to the development of antimicrobial resistance. Infectious diseases are periodically emerging and re-emerging in nearly every corner of earth, many with the potential to cause pandemic [1,2].

The impact of the emerging and re-emerging diseases has been enormous at socio-economic and public health levels and it presents a great challenge for the future [3,1].

While the world is facing many public health threats, the World Health Organization (WHO) in 2015, has compiled a list of top emerging pathogens likely to cause severe diseases with potential to generate a public health emergency, and for which no, or insufficient, preventive and curative solutions exist.

WHO's initial list of diseases needing urgent attention includes: 1. Crimean Congo haemorrhagic fever; 2. Filovirus diseases (Ebola); 3.4. *Highly pathogenic emerging Coronaviruses* relevant to humans (MERS CoV- Middle East respiratory syndrome coronavirus & SARS- Severe acute respiratory syndrome); 5. Lassa Fever; 6. Nipah virus disease; 7. Rift Valley Fever. Also listed were three other diseases were designated by WHO as "serious," requiring attention "as soon as possible": 8. chikungunya, 9. severe fever with thrombocytopenia syndrome, and 10. zika [4].

WHO said that other diseases with epidemic potential – such as HIV/AIDS, tuberculosis, malaria, avian influenza, and dengue – were not included in the list because there are major disease under control. According to WHO, the list will be reviewed annually or when new diseases emerge.

So, World Health Organization has compiled a list of the top 10 threats to global health to focus on in 2019. The list contains a number of serious issues from climate change to inadequate health care facilities: 1. Air pollution and climate change, 2. Noncommunicable diseases, 3. Global influenza pandemic, 4.Fragile and vulnerable settings, 5. Antimicrobial resistance, 6. Ebola and other high-threat pathogens (MERS- Co V & SARS, etc.), 7. Weak primary health care, 8. Vaccine hesitancy, 9. Dengue and HIV [5]. As can be seen, infectious diseases dominate WHO's list of 2019 health threats-more than half of the list is made up of emerging infectious diseases.

An emerging infectious disease (EIDs) is one that has appeared and affected a population for the first time, or has existed previously but is rapidly increasing, either in terms of the number of new cases within a population, or its spread to new geographical areas. Also grouped under emerging infectious diseases are those that have affected a given area in the past, declined or were controlled, but are again being reported in increasing numbers. Sometimes an old disease appears in a new clinical form that may be severe or fatal and these are known as re-emerging diseases [6, 7].

Emerging and re-emerging infectious diseases are a significant threat to global health security. Experiences shows that outbreak of these diseases could not only potentially cause a large number of human deaths, but also have huge social and economic impact worldwide. Many of these diseases do not yet have any cure [8].

There has been an extensive progress in the prevention, control and even elimination of some emerging infectious diseases, but however, they still remain a major public health concern, in view of the associated high morbidity and mortality **[1].**

On 31 December 2019, WHO was informed of cases of pneumonia of unknown cause detected in Wuhan City, Hubei Province of China [9]. From 31 December 2019 through 3 January 2020, a total of 44 case-patients with pneumonia of unknown etiology were reported to WHO by the national authorities in China. During this reported period, the causal agent was not identified **[10].** On 11 and 12 January 2020, WHO received further detailed information from the National Health Commission China that the outbreak is associated with exposures in one seafood market in Wuhan City. The Chinese authorities identified a novel (new) type of coronavirus, which was isolated on 7 January 2020. On 12 January 2020, China shared the genetic sequence of the novel coronavirus for countries to use in developing specific diagnostic kits [11].

The World Health Organization has confirmed COVID-19 (a shortened version of coronavirus disease 2019) as the name of the disease that CoV infection causes. Prior to this, the virus and/or disease was known by various names including novel coronavirus (2019-nCoV), 2019-nCoV, or variations on this [12].

Coronaviruses (CoV) are a large family of viruses that cause illness ranging from the common cold to more severe diseases such as Middle East Respiratory Syndrome (MERS-CoV), that was first identified in Saudi Arabia in 2012 and Severe Acute Respiratory Syndrome (SARS-CoV) [13]. A novel coronavirus (nCoV) is a new strain that has not been previously identified in humans.

Coronaviruses are zoonotic, meaning they are transmitted between animals and people. Common signs of infection include respiratory symptoms, fever, cough, shortness of breath and breathing difficulties. In more severe cases, infection can cause pneumonia, severe acute respiratory syndrome, kidney failure and even

death. Standard recommendations to prevent infection spread include regular hand washing, covering mouth and nose when coughing and sneezing, thoroughly cooking meat and eggs. Avoid close contact with anyone showing symptoms of respiratory illness such as coughing and sneezing [14].

On 13 January 2020, the Ministry of Public Health, Thailand reported the first imported case of lab-confirmed novel coronavirus (2019-nCoV) from Wuhan, Hubei Province, China. On 15 January 2020, the Ministry of Health, Labour and Welfare, Japan (MHLW) reported an imported case of laboratory-confirmed 2019-novel coronavirus (2019-nCoV) and on 20 January 2020, National IHR Focal Point (NFP) for Republic of Korea reported the first case of novel coronavirus in the Republic of Korea [11]. Person-to-person spread has been confirmed, but it is uncertain how easily the virus spreads between people. Clinical trials and investigations to learn more about the virus, its origin, and how it affects humans are ongoing.

As of 20 January 2020, 282 confirmed cases of 2019-nCoV have been reported from four countries including China (278 cases), Thailand (2 cases), Japan (1 case) and the Republic of Korea (1 case). Cases in Thailand, Japan and Republic of Korea were exported from Wuhan City, China [10].

The situation of Covid-19 is rapidly evolving with case counts and deaths increasing each day. WHO assesses the risk of this event to be very high in China, high at the regional level and high at the global level [15]. On January 30, the World Health Organization announced that the novel coronavirus disease, COVID-19, was a public health emergency of international concern, as latest figures show that 9,826 people have been infected and 213 have died [15].

Cases have been reported and in 26 countries outside of China. On February 20, globally 75 748 cases are confirmed, and 2121 deaths. On this period, outside of China are confirmed 1073 cases infected and 8 deaths [16].

WHO is working with researchers and other experts to coordinate global work on surveillance, epidemiology, modelling, diagnostics, clinical care and treatment, and other ways to identify, manage the disease and limit onward transmission. WHO is working with global experts, to rapidly expand scientific knowledge on this new virus, and to provide advice to countries and individuals on measures to protect health and prevent the spread of this current outbreak. WHO prepared disease commodity package for supplies necessary in identification and management of confirmed patients; provided recommendations to reduce risk of transmission from animals to humans; updated the travel advice for international travel in health in relation to the outbreak; utilizing global expert networks and partnerships for laboratory, infection prevention and control, clinical management and mathematical modelling; activation of R&D blueprint to accelerate diagnostics, vaccines, and therapeutics. WHO has been in regular and direct contact with country authorities since the reporting of these cases [10].

WHO is also informing other countries about the situation and providing support as requested and countries have shared information with WHO under the International Health Regulations. The SARS outbreak in 2002 led to the formation of new International Health Regulations-IHR 2005, with purpose and scope to prevent, protect against, control and provide a public health response to the international spread of disease [17].

In the first days after the coronavirus outbreak became known, a lot of international scientific journals, publishers, funders and scientific societies signed a joint statement that confirmed that all articles and resources relevant to the coronavirus are made immediately open access, or freely available at least for the duration of the outbreak. This based on WHO Statement on developing global norms for sharing data and results during public health emergencies [18]. Scientists and medical professionals around the globe have been relying on freely available studies, resources, and datasets to quickly inform treatment strategies, public health initiatives, etc. Research findings are made available via preprint servers before journal publication, or via platforms that make papers openly accessible before peer review, with clear statements regarding the availability of underlying data.

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