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Pre/post-surgical investigation of some angiogenic factors due to cancer and obesity

Secondary primary malignancy presence and related factors in chronic lymphocytic leukemia

Examination of Clinical and Demographic Characteristics of 14 Cases with Frontal Fibrosing Alopecia

Complete heart block and acute inferior myocardial infarction due to generalized vasospasm

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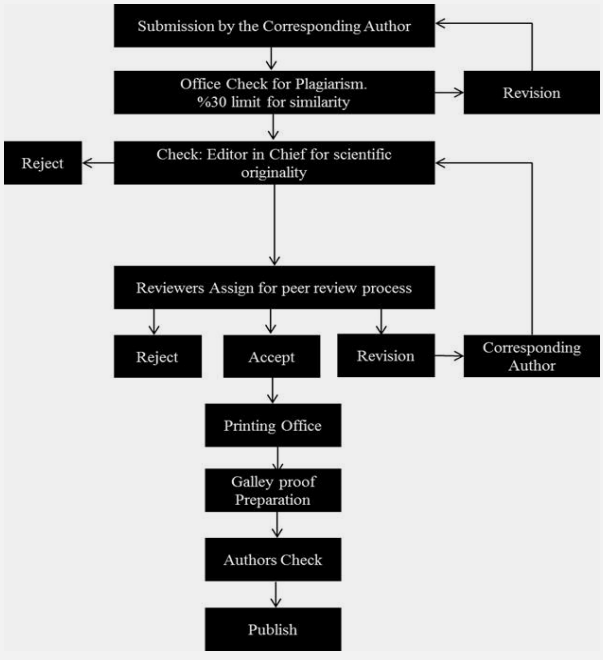

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Pre/post-surgical investigation of some angiogenic factors related with cancer and obesity

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Abstract

Objective: Obesity is one of the important health problem for developed and developing countries. Due to literature some obesity related factors may trigger the tumor formation. For tumor development, tumoregenic cell and tissue needs to oxygen and nutrients. Once the tumor has developed, it stimulates the angiogenesis by producing chemical signals and grows by supplied oxygen and nutrients with newly formed vessels. Aim of this study is to compare some angiogenic factors before and after surgery which will supply more information about the link between the cancer and obesity.

Material and Methods: Serum samples were obtained before and 48 hours after surgery. Adrenomedullin, vascular endothelial growth factor, hipoxia inducible factor1-α and matrix metallo proteinase-2 levels were investigated in cancerous and noncancer patients. Angiogenic factors were assayed by ELISA method.

Results: Higher levels of angiogenic factor were detected in cancer tissues more than in non-cancer tissues, in pre-obese and obese patients. It is seen that in humans, in post-operated patients angiogenic factors are higher in obese individuals, while non-cancer patients are also higher in obese groups and angiogenic factors which stimulate angiogenesis.

Conclusion: In the treatment of cancer, as defined previously the anti-angiogenic factors should be considered and applied as epigenetic phenomen. Due to our finding cancer related elevated angiogenic and growth factor biochemicals had been also increased in obes population and in cancer patients with surgical intervention. In the light of literature and our findings, instead of drugs, radiation therapy or surgery, which have many side effects in the treatment of cancer, we need to focus to this epigenetic phenomen for cancer patients. In general, we can say that both obesity and surgical applications lead to an increase in angiogenic factor levels, and that the healing process of wounds causes a marked increase in angiogenic factor levels

Keywords: Angiogenic Factor, Surgery, Obesity, Cancer

Introduction

Vessel formation is a process which starting with embryonic stage and is an ongoing process not only in a healthy state but also in disease states such as cancerogenous. Vessel formation, that is, angiogenesis, is caused by the sprouting of new blood vessels from endothelial precursor cells. Signal, may come from embryonic development, wound healing or the tumor cell (1). In adult organisms, angiogenesis is necessary for many processes such as wound healing, growth, sex hormone releasing and formation of vessel tissue during pregnancy (2,3). Also tissue hypoxia causes sprouting angiogenesis and budding of a new capillary sprout laterally from a preexisting vessel (4,5). Briefly vasculogenesis is de novo formation of blood vessels from endothelial cell procursors (6). The World Health Organization defines obesity as an accumulation of excess fat tissue that causes a risk to health. According to the World Health Organization (WHO 1998) (7), individuals with Body Mass Index (BMI) over 30 evaluates as obese. Overweight and obesity are seriously risk factors for a number of chronic diseases, including diabetes, cardiovascular diseases and cancer. Once considered a problem only in high income countries, overweight and obesity are now dramatically on the rise in low- and middle-income countries, particularly in urban settings. The National Cancer Institute states that there is a strong relationship between elevated BMI in men and an increased risk of colerectal cancer. Obesity is also associated with increased risks of the

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following cancer types, and possibly others as well; esophagus, pancreas, colon and rectum, breast (after menopause), endometrium, kidney, thyroid, gallbladder. Angiogenesis is inevitable necessary for tumor growth and methasthasis of tumor cells to distant locations. Hypoxia is a critical process for tumor angiogenesis and is carried out primarily by the transcription of hypoxia-sensitive genes and HIF (8). Several mechanisms were considered for vascularization of tumors including endothelial sprouting and bone marrow-derived endothelial cells and so forth. Endothelial sprouting is a process that is controlled by balance between ″pro- and anti-angiogenic″ factors. Endothelial sprouting is a basic mechanism for tumor vascularization. During sprouting, pericytes detach and blood vessels dilate and the process is under control of VEGF and angiopoietins (9). During bone marrow-derived endothelial cell process, circulating cells in the peripheral blood may participate in vessel formation (10). The purpose of our work is to examine the levels of some angiogenic factors in pre- and post-operative individuals with and without obese and cancer and non-cancerous individuals.

The gelatinases (MMP-2 and MMP-9) are subsequently enriched by a region of three-fi bronectin type II repeats within their catalytic domains. Those two enzymes are responsible for the final degradation of fibral collagens after initial cleavage by collagenases (11). Many publications link increased expression of gelatinases as key proteases with malignant tumor ability to metastasis. According to cancer development data, degradation of extracellular matrix is crucial for malignant tumor development and spread and thus has an indispensable role in prognosis and selection of the therapy method. Detection of active MMP-2 (e.g. in circulating blood) could be more sensitive than other, well-established methods (12). Human matrix metalloproteinases (MMPs, matrixins) are a family of over 20 different endopeptidases that are able to degrade various components of the extracellular matrix (ECM). There are several preclinical research publications confirms MMP-2 involvement in to all human cancers. A high level of MMP-2 has been shown to predict adverse outcome in patients with gastric, pancreatic, and prostate cancers (13). Proteins of the matrix metalloproteinase (MMP) family are involved in the breakdown of extracellular matrix (ECM) in normal physiological processes, such as embryonic development, reproduction, and tissue remodeling, as well as in disease processes, such as arthritis and metastasis. VEGF is a signal protein produced by cells that stimulates vasculogenesis and angiogenesis. It is part of the system that restores the oxygen supply to tissues when blood circulation is inadequate such as in hypoxic conditions (14). VEGF's normal function is to create new blood vessels during embryonic development, new blood vessels after injury, muscle following exercise, and new vessels (collateral circulation) to bypass blocked vessels. The overexpression of VEGF is a contributing factor to the development of disease. For example, solid tumors require an increased blood supply if they are to continue growing beyond a certain size and tumors that express VEGF are able to continue growing because they can develop this enhanced blood supply, a process referred to as angiogenesis. Cancers that express VEGF are therefore able to grow and spread (metastasize) to other organs and regions of the body. Hypoxia-inducible factor-1 (HIF1) is a heterodimeric transcriptional complex and important molecule in the regulation of oxygen levels in mammals, especially in hypoxic tissues (15,16). Increase of HIF-1α transcription is considiring the result of hypoxia-stimulation (17). HIF-1α is a transcription factor that is involved in tumor growth and methasthasis, especially in response to hypoxia. In some studies, results has been shown that HIF-1α protein expression increased in some human cancer types (18). The proliferation of cancer cell reflects the rate of angiogenesis, cancer cell proliferation causes hypoxia in the tissue, and cellular adaptation to hypoxia is the key step in the formation of the tumor. This adaptation is regulated by HIF-1α and plays an important role in oxygen homeostasis (15). Adrenomedullin (AdM) is a multipotentially, regulatory peptide that was first isolated from human pheochromocytoma extracts by Kitamura et al. (1993) (19). AdM is synthesized both by tumour cells and by normal adrenal medulla cells, as well as by many other tissues including macrophages, mast cells, endothelial, and vascular smooth muscle cells. (20). It has also as a local paracrine and autocrine functions with multiple biological activities such as vasodilatation, cell growth, regulation of hormone secretion, natriuresis, and antimicrobial effects (21). Larrayoz et al. (2014) have been stated that adrenomedullin increased tumor cell proliferation, stimulated angiogenesis, and suppressed the immune system. Adrenomedullin is also activated by HIF and it has been considered essential for survival of tumor cells (22).

Material and method

Serum samples were obtained from 25 cancer patients and 22 non-cancer patients before and 48 hours after surgery. Approximately 5 ml of blood was collected in EDTA- or heparin-containing tubes. Samples were centrifuged at 8000 g for 15 min, followed by collection of the plasma. Plasma samples were stored at 80 oC until elisa assays were performed. In our study, serum samples were taken from 9 obese, 7 pre-obese and 9 normal-weight cancer patients and non-cancer patients in 10 obese, 7 pre-obese and 5 normal weights. Adrenomedullin (AdM) vascular endothelial growth factor (VEGF), hipoxia inducible factor-1 alpha (HIF1-α) and matrix metallo proteinase-2 (MMP-2) levels were investigated for all cases. Angiogenic factor levels were assayed colorimetrically by ELISA kits(AdM; CK-30105,

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Hangzhou Eastbiopharm Co., Ltd. VEGF; EK0540 Booster Biological Technology Ltd, MMP-2; ER0051, Fine Test, HIF1-α; ER0191, Fine Test) (23). Analysis of angiogenic factors in serum samples from patients was performed at Inonu University Molecular Biology Laboratory. Differences in results between pre-op/post-op and cancer/noncancer groups were analyzed using an unmatched Student t test. p value < 0.05 was considered statistically significant.

Results

Angiogenic factor levels are shown in Table 1. According to Table 1, it is seen that angiogenic factor levels are about 2-fold increased, especially in cancerous in blood serum samples of cancer patient. Similarly, angiogenic factor levels increase after surgery. Adrenomedullin and HIF1-α levelsin post-op cancer group increased when compared to other groups. Especially in patients with cancer, an increase of about 50% compared to those without cancer was detected. However, MMP-2 and VEGF levels increased by 90-100% in post-op cancer group compared to pre-op cancer group. When the increases observed in angiogenic factor levels in the obese group were compared proportionally, a more significant increase was observed in cancer patients. Especially, VEGF, MMP-2 and HIF1-α levels in cancer patients after surgery increased two-fold compared to normal weight; it was 1.4 times more in obese groups of non-cancer patients (Table 1, Figure 1-4).

The highest ADM level was found to be 332,85 ± 8,52 ng /l as the result of surgical application in cancer patients and obese individuals (P <0,05). ADM levels were found to be higher in non-cancer but obese individuals (Figure 1). VEGF levels have also increased after surgery in cancer and obese patients, as in ADM levels. VEGF level was 238,39 ± 12,23 ng / l after surgery in cancer and obese patients (P <0,05) (Figure 2). MMP-2 levels in cancer and obese patients after surgery increased two-fold compared to pre-operative and normal weight patients. MMP-2 levels were 40.02 ± 2.07 ng / L (P <0.05), 18.05 ± 1.05 ng / l and 19.56 ± 1.22 ng / l, respectively (Figure 3). HIF1-α level was measured as 182,67 ± 4,92 (pg / l) in cancer and obese group after crush application (P <0,05) (Figure 4). Similarly, there was an increase in angiogenic factor levels after the operation. Proportionally, the highest increase was observed in VEGF and HIF levels in cancer patients. These results indicate that the angiogenic factor levels are increased due to the healing process of surgical wound healing after surgery.

Table 1: Angiogenic factor levels

Adrenomedullin Levels (ng/l)				
	Cancer		**Non-Cancer**	
Groups	Pre-op	Post-op	Pre-op	Post-op
Obese	199,91±5,57	332,85±8,52*	187,12±7,42	262,02±11,02*
Pre-obese	142,66±4,76	262,85±6,21	161,90±6,27	245,60±10,56
Normal Weight	118,32±4,32	197,79±9,07	126,65±6,35	191,56±8,15
Vascular Endothelial Growht Factor Levels (ng/l)				
Groups	Pre-op	Post-op	Pre-op	Post-op
Obese	119,04±5,22	238,39±12,23*	82,43±5,26	121,55±7,54*
Pre-obese	93,17±3,88	182,45±10,08	66,39±3,88	98,29±5,55
Normal Weight	66,92±4,32	116,46±8,45	54,95±3,05	87,93±4,27
Matrix Metalloproteinase-II Levels (ng/l)				
Groups	Pre-op	Post-op	Pre-op	Post-op
Obese	18,05±1,05	40,02±2,07*	11,27±0,89	17,42±1,22*
Pre-obese	14,40±2,31	32,61±1,85	9,63±1,21	14,61±0,84
Normal Weight	10,87±1,52	19,56±1,22	8,75±0,76	13,22±0,69
Hipoxic Inducible Factor1-α Levels (pg/l)				
Groups	Pre-op	Post-op	Pre-op	Post-op
Obese	85,39±2,47	182,67±4,92*	83,26±3,68	121,08±5,27*
Pre-obese	72,51±2,09	149,23±5,12	70,50±3,08	112,63±5,18
Normal Weight	57,01±1,64	99,46±5,08	56,13±2,88	90,08±4,85

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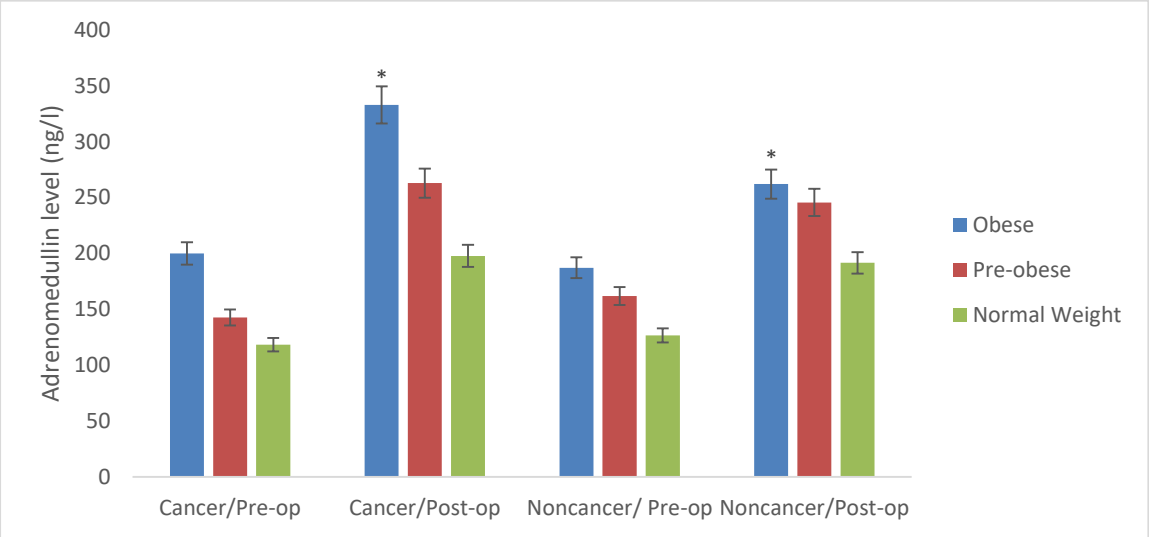

Figure 1: Adrenomedullin levels (*Significant on 0,05 levels).

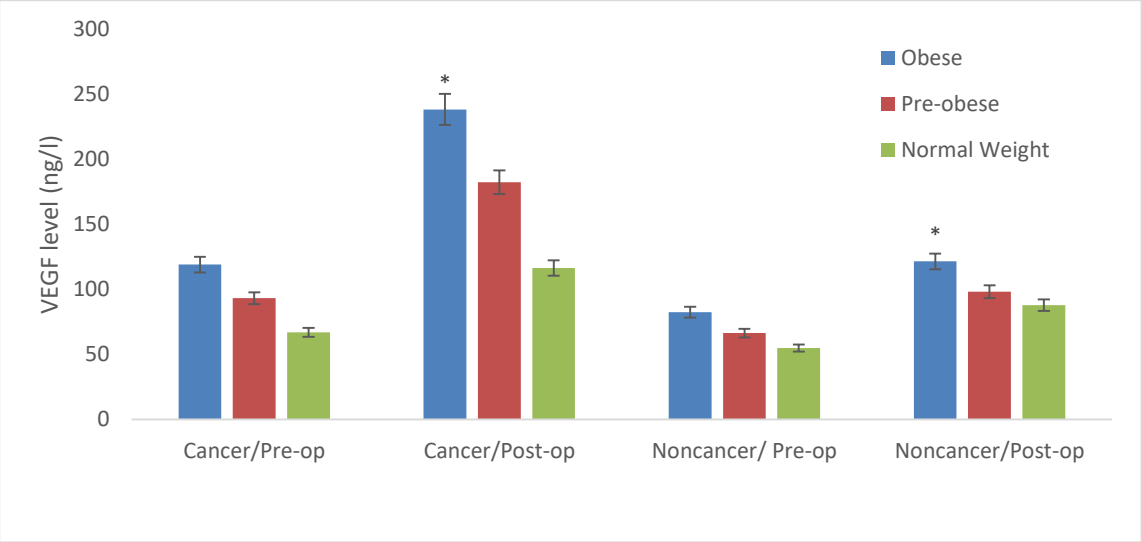

Figure 2: VEGF levels (*Significant on 0,05 levels).

Discussion

Numerous studies have been performed to reveal the relationship between surgical intervention and angiogenic factor release. Belizon et al. (2006) (24), Kong et al. (2010) (25) reported significant increases in postoperative VEGF levels in their study. Jarmila et al. (2004) (26) reported that surgery is a condition that stimulates angiogenesis and causes the release of many angiogenic factors.

For tumor development, it needs oxygen and once the tumor has developed it stimulates the formation of new blood vessels by producing chemical signals and grows by providing more oxygen and nutrients with newly formed vessels. Angiogenesis is a process that involves many steps.

This means that every step in this process is a potential target for new cancer treatments. The hope here is that the tumor can not get enough nutrients and oxygen to reach the end hunger and death. Inhibitors of angiogenesis or anti-angiogenic drugs may play an important role in the treatment of certain types of cancer by inhibiting new blood vessel formation. It should be thought that drugs can show their effect here in the epigenetic process. Angiogenic factors can contribute to tumor formation while providing vascularity for the organism. For example, it is now well known that adrenomedullin is a peptide with multiple effects and it may have a protective function as antioxidant, but it may also cause harmful effects by participating in tumor angiogenesis. The need for

organisms to be regulated in such a way as to bring about positive effects of these chemical molecules will accelerate their efforts to inhibit the formation of new blood vessels, which contribute to the development and spread of cancer. As a result, surgical operations, chemotherapy, and radiotherapy treatments will contribute significantly to molecular-physiological measures.

Hypoxia inducible factor 1-alpha (HIF 1-a) is particularly found in obesity, with a body mass index of 30 and above; Due to the increase of the body mass, the formation of oxygen-free environment will cause this factor to be released and oxygen and nutrients will be provided by the formation of new veins in the tissues. Matrix metallo proteinase enzymes contribute to the formation of new blood vessels by weakening the blood vessel wall, while VEGF also provides new blood vessel formation as a growth factor. Other angiogenic factors such as these also provide vascularity. The important difference is that if the tumor formation starts in some way for some reason, the resulting tumor becomes an uncontrollable growth that negatively affects the life of the living by using this system which is not alien to itself. The mission of researchers should be to prevent the tumor from abusing this system that the organism possesses.

Recent studies suggest anti-anjiogenic factors may be used in the treatment of cancer. Clinical experience suggests that anti-angiogenic therapy is a valid approach to medicine, but that it needs to work harder to make it realistic (27-29).

While the matrix metalloproteinase enzyme causes the destruction of adrenomedullin, hypoxia causes an increase in adrenomedullin (22). Hypoxia may develop due to obesity (30), which is expected to increase in adrenomedullin level; It is expected that the increased MMP-II enzyme due to tumor formation will also destroy adrenomedullin. This reflects a paradoxical situation. In our study, also more adrenomedullin and VEGF were detected in cancerous tissues. As we mentioned earlier, angiogenesis is a process that emerges with the unification of many steps and this process can explain the paradoxical situation.

Conclusion

The angiogenesis process is a convergence of many steps. This means that each step in this process is a potential target for new cancer treatments. The hope here is that the tumor will be disappear depending on the lack of nutrients and oxygen. Rationalized antiangiogenic process should be considered additional vehicle in the treatment of cancer. In the light of literature and our findings, instead of drugs, radiation therapy or surgery, which have many side effects in the treatment of cancer, we need to focus to this epigenetic phenomen for cancer patients.. In our study, we compared preoperative and postoperative levels of some angiogenic factors in non-cancer and cancerous and non-obese and obese individuals We are postulating that the angiogenesis process should be evaulated as an independent parameter. Because the organism will effort to maintain its instinctual life in every adverse situation and will continue the angiogenesis process for the life of the tissues, regardless of the disease or health. More importantly, it is to be thought that the angiogenesis process can be used more effectively, in cancer cases. Antianogenogenic factors may also affect normal tissues with the tumor, so it is important to consider studies that would inhibit blood transfusion to other tissues outside the tumor tissue.

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Author's Contributions: M.Y. Research concept and design; **SAG, AY, NZC, GP, TS, OCT, MY:** Patients Surgical Procedures, data collecting, biochemical analysis and interpretation of data, **MY, SAG:** Manuscript preparation; **MY:** Revisions. All authors approved the final version of the manuscript,

Ethical issues: All Authors declare that Originality of research/article etc... and ethical approval of research, and responsibilities of research against local ethics commission are under the Authors responsibilities. The study was conducted due to defined rules by the Local Ethics Commission guidelines and audits.

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Complete Heart Block and Acute Inferior Myocardial Infarction Due to Generalized Vasospasm

Yahya Kemal Icen[1*], Mevlut Koc[1]

Abstract

Objective: Sixtyone years old female patient had applied to emergency department with chest pain. Her ECG taken was compliant with acute inferior myocardial infarction and complete heart block. In her coronary angiography (CAG), there was generalized vasospasm from osteal in left anterior descending coronary artery (LAD) and circumflex artery (CX). 10 mcg/kg/mn nitrate was infused in the coronary and vasospasm is disappeared. After CAG, her ECG was normal and she discharged with medical treatment recommendations

Keywords: Complete Heart Block, Generalized Vasospasm, Coronary

Introduction

The spasm in coronary arteries may cause a wide spectrum of cardiac cases from temporary chest pain to acute ST elevation myocardial infarction (STEMI)1. Despite vasospasm is usually resolved with nitrate and nitrate derivatives, sometimes cardiologists may encounter some refractory cases2,3. If the vessels with vasospasm feed the sinoatrial or atrioventricular nodes, brady-arhythmic complications may develop in the patient4. In this case, we have submitted a patient with complete heart block due to generalized vasospasm.

Case: the 61 years old female patient had applied to emergency department with retrosternal chest pain. Hypertension and smoking history were present in her history. In the CAG of the patient applied one month before, the presence non-critical lesions were reported. In her physical examination, there were no finding except the pulse of 35 pulse/minute. In the ECG taken; ST segment elevation and complete heart block were present at D2, D3, AVF derivations (figure 1). The patient was diagnosed as acute inferior myocardial infarction and complete heart block and she was hospitalized at coronary intensive care unit (CICU). Due to the non-critical obstructions in the previous CAG, vasospasm was considered and nitrate infusion at a dose of 5 microgram/kilogram/minute was started. In the assessment of echocardiography, inferior wall was observed as hypokinetic and ejection fraction was measured as 55%. The patient, whose general status was impaired, was taken to the CAG unit.

In the CAG result, it was found that there was a left anterior descending artery (LAD) and circumflex artery (CX) was completely obstructed from osteal (figure 2) and there were plaques in the right coronary artery (RCA) (figure 3). Nitrate dosage was increased to 10 mcg/kg/minute then the completely occluded regions in LAD and CX had opened (figure 4). She was taken to the CICU and in her ECG taken, it was observed the ST segment elevation had disappeared and it was at the sinus rhythm (figure 5). The patient, who was monitored at CICU for one day and at cardiology service for 2 days, was discharged with nitrate, diltiazem, acetylsalicylic acid and atorvastatine. Drug treatment was continued at her outpatient polyclinic follow-ups.

Discussion

In the ECG of our patient, despite the ST elevation in inferior derivations and a complete heart block, we considered vasospasm due to the non-critical obstructions in the previous CAG one month ago and thus, we did not apply CAG instantly. Firstly, we had waited to have vasospasm dissolve via nitrate infusion at CICU. In the literature; it is specified that a female patient had a recurrent completely heart block due to coronary vasospasm and thus a permanent pacemaker was placed. In another patient, as a result of spontaneously developed generalized vasospasm; the development of complete heart block, cardiogenic shock, ventricular fibrillation and ischemic stroke was mentioned.

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In a series of three cases; DDD-R permanent pacemaker with an intracardiac defibrillator (ICD) was placed to the patients at whom high-grade heart block and cardiac arrest occurred due to vasospasm7. Again in another case, a permanent pacemaker was placed due to bradyarrhythmia caused by vasospasm8.

In our patient, the nitrate dosage given at CICU was not quite efficient. We have taken out patient to CAG unit due to the impairment in her general status. As a result of intra-coronary nitrate infusion, vasospasm was dissolved..

The patient was discharged with medical recommendations. Contrary to most of the patients in the literature, there was no need for a permanent pacemaker in her outpatient follow-ups

Conclusion

In coronary vessels, general vasospasm can cause acute inferior myocardial infarction and complete heart block. In these patients, vasodilatory therapy may be tried before invasive treatment.

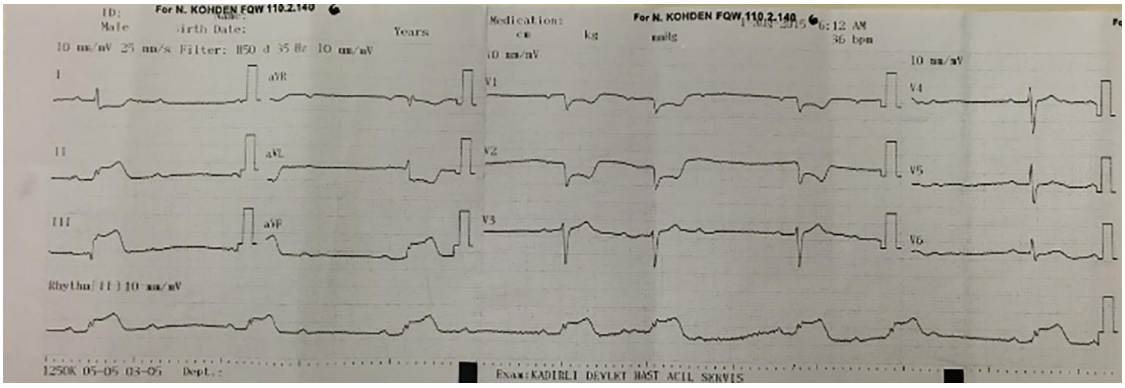

Figure 1: Complete heart block and acute inferior myocardial infarction in 12 lead surface ECG

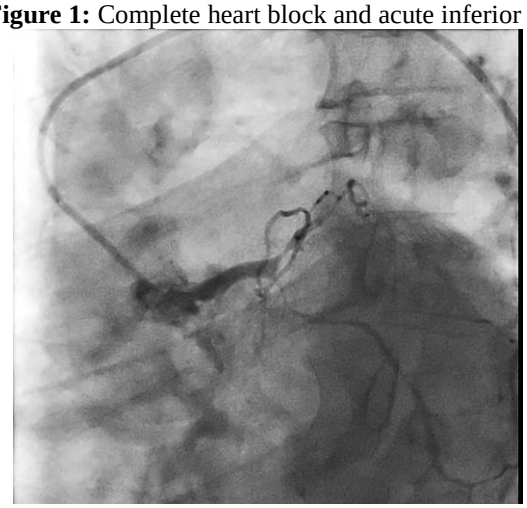

Figure 2: Generalize vasospasm in LAD and CX

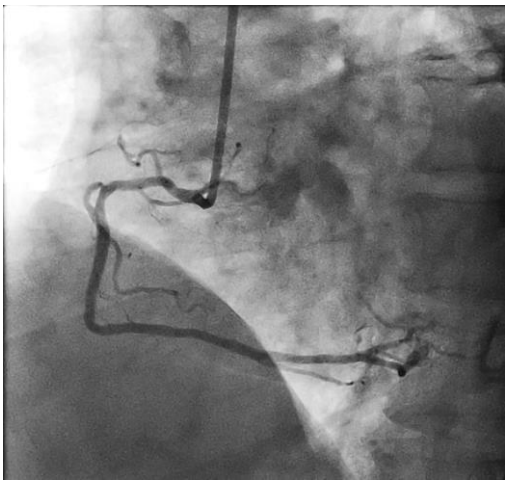

Figure 3: Non-critical plaque in RCA

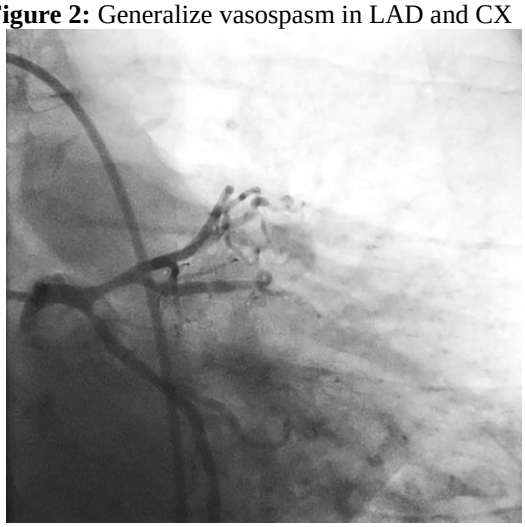

Figure 4: Resolving vasospasm after 10 mcg/kg/minute nitrate infusion

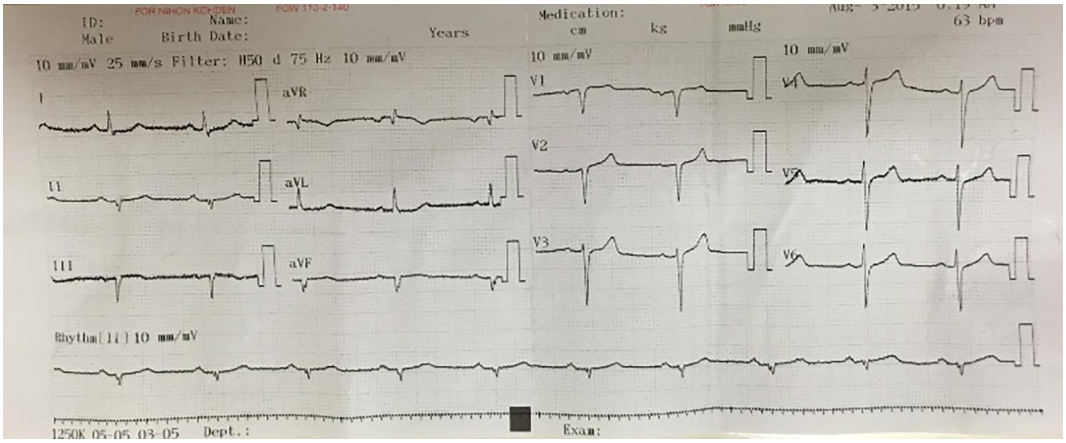

Figure 5: Resolution ST elevation and sinus rhythm in 12 lead surface ECG

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Secondary Primary Malignancy Presence and Related Factors in Chronic Lymphocytic

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Abstract

Objective: The secondary primary malignancy frequencies have seen increased in chronic lymphocytic leukemia (CLL) regardless of therapy. The aim of this study was to investigate the frequency of secondary primary malignancy in patients followed with the diagnosis of chronic lymphocytic leukemia.

Materials and Methods: The 183 patients with diagnosed of CLL were enrolled into this study. The data of the patients were evaluated retrospectively. Patients diagnosed with CLL were categorized according to age, gender and presence or absence of additional malignancy. Patients with CLL and concomitant malignancy were compared with other patients.

Results: Fifty four patients (29.5%) were female and 129 (70.5%) were male. Secondary primary malignancy was detected in 9 (%4,9) patients. CD5 positivity was found in all of the patients with malignancy and in 91% of whole patients. 5.4% of males and 3.7% of females had solid organ tumors with CLL. Although the proportion of solid tumors was higher in males, this difference was not statistically significant ($p = 0.847$). The mean age of cases with secondary malignancy was statistically significantly higher than that without secondary malignancy ($p < 0.05$).

Conclusion: In our study, all of the patients with the second primary malignancy were CD5 positive. BCL2 proto-oncogene levels were found increased in CD5-positive CLL cells, not in normal B cells those were positive for CD5. In vitro studies showed that, B-CLL cells with higher BCL2 levels survive is longer than cells with lower BCL2 levels. Presence of the secondary malignancy except CLL may be related with BCL2 increment as well as CD5 positivity. We need more comprehensive studies to determine the relationship between the presence of BCL2, CD5 positivity and secondary malignancies.

Keywords: Chronic lymphocytic leukemia, Secondary primer malignancy

Introduction

Chronic lymphocytic leukemia (CLL) occurs primarily in older adults, the average age of patients is approximately 70th. However, it may occasionally develop between the ages of 30-39. CLL is the most common type of leukemia in adults in Western countries, and occurrence is about 25-30% of all leukemia cases (1). Chronic lymphocytic leukemia is a B cell neoplasm, which one of the B cell chronic lymphoproliferative disorders. B cell CLL is considered a small lymphocytic lymphoma that presents differently (2), and is characterized by the accumulation of monoclonal lymphocytes with functional impairment. Although the asymptomatic phase has little effect on patients' quality of life, progression of the disease at later stages results in increased hospitalization and morbidity rates. Among the most common causes of death are systemic infections, haemorrhage, and wasting due to cachexia. While quite rare, spontaneous clinical regression has been reported (3). The most characteristic finding of CLL is lymphocytosis in peripheral blood and bone marrow, and a persistent absolute lymphocyte count > 5000/μL, which is important for the diagnosis of CLL. The most common clinical findings are lymphadenopathy, splenomegaly, and hepatomegaly (4, 5). A number of retrospective studies have reported that CLL patients are at increased risk of developing other hematological and solid organ tumors. Malignancies such as lung, breast, colon, and prostate cancers have been reported to be frequently observed in non-CLL populations. The etiopathogenesis of the increase in frequency in other tumors seen in cases of CLL is as yet unclear (6, 7). In cases of CLL, the second primary tumor shows an increase in frequency independent of the treatment. In a comprehensive study, other malignancies were detected in 11% of CLL patients.

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This risk has been observed to be greater for Kaposi's sarcoma, malignant melanoma, laryngeal cancer, and lung cancer (8). In a large-scale analysis of a population of 2.3 million breast, colorectal, prostate, lung, kidney, pancreatic, and ovarian cancer patients, 19% had previously been diagnosed with CLL.

Material and method

Our study population consisted of 183 chronic lymphocytic leukemia patients whose cases were monitored in the clinic of the Hematology Department at Yüzüncü Yıl University Faculty of Medicine Hospital (Van, Turkey) between 2010-2017. Patient files and data entered in the hospital records system were reviewed retrospectively. Patients were categorized according to age, gender, and the presence of other malignancies along with the diagnosis of CLL. Patients with other malignancies were compared to those without.

Statistical analysis: The SPSS 19.0 package program was used for statistical analysis of the data. Numerical measurements were specified as mean, maximum, and minimum, and categorical measurement as number and percentage. The independent samples T test was used to examine the relationship between categorical measurements. The level of statistical significance was .05 for all tests.

Results

The present study included 183 patients, 54 (29.5%) women and 129 (70.5%) men. Secondary malignancy was detected in 9 (4.9%) patients, of whom two were female and seven male. The mean age of those without a secondary malignancy was 67.6 years (34 - 96) and that of those with a secondary malignancy was 75.6 years (52 - 89).

While the rate of CD5 positivity was %91 in whole study patients, this rate was %100 in patients with Secondary Malignancy. Of the patients with malignancies, esophageal cancer was detected in 3 patients, lung cancer in 3, stomach cancer in 1, skin cancer in 1, and prostate cancer in 1 patient.

In 5.4% of males and 3.7% of females solid organ tumors were present along with CLL. Although the percentage of males with solid tumors was higher, the difference was not statistically significant (p = .847).

The mean age of cases with secondary malignancy was statistically significantly higher than those without (p < .05) (Table I).

Table 1. General characteristics of all study patients

		All Patients	CLL cases without second primer malignancy	CLL cases with Secondary Primer Malignancy
Number (n)		183	174 (%95,1)	9 (%4,9)
Age (year)		68 (34-96)	67,6 (34-96)	75,6 (52-89)
Gender	**Female**	54 (%29,5)	52 (%96,3)	2 (%3,7)
	Male	129 (%70,5)	122 (%94,6)	7 (%5,4)
Type of Malignancy			Esophageal cancer	3 (%33,3)
			Lung cancer	3 (%33,3)
			Skin cancer	1 (%11,1)
			Prostate cancer	1 (%11,1)
			Gastric cancer	1 (%11,1)

Discussion

Previous studies have determined that the most common cancers in our region (eastern Turkey) are gastric, skin, and bladder cancers in men, and esophageal, stomach, and breast cancers in women (10). In our study, the malignancies most frequently accompanying CLL were lung and esophageal cancers. The next most common malignancies were stomach, skin, and prostate cancers. One study reported other malignancies in approximately 10% of CLL patients during the course of the disease (11). In the present study, the second primary malignancy rate was 4.9%. Of the second primary malignancy cases, 22.2% were female and 77.8% were male; thus, 3.7% of the women and 5.4% of the men had a second primary tumor. Although the percentage of males with a second primary tumor was greater, the difference was not statistically significant. Some studies have determined that older age and male sex are active factors in the risk of developing new cancer in CLL cases (6). In the present study, the mean age of the patients with other malignancies (75.6) was significantly greater than the mean age of those without (67.6).

In addition, the growth of solid tumors concurrent with CLL suggests the role of possible immunological disorders (7). A total of 90% of CLL lymphocytes are of B cell origin. Although the percentages of T cells and natural killer cells do not vary, an increase in the absolute T cell count can be observed and the function of natural killer cells is diminished. B cell CLL (B-CLL) patients have a T cell subpopulation with lower levels of CD4 or CD8 than classical T lymphocytes. This may result from a nonclassical T cell developmental pathway or B cell interaction (12-15).

These types of T cells have been described in some autoimmune diseases (12). Various gene mutations have been identified that have been determined to affect tumor suppressor genes, oncogenes, DNA damage repair (ATM, TP53), RNA decay (SF3B1, DDX3X) and cell signaling pathways (NOTCH1, FBXW7), and inflammation pathways (MyD88, DDX3X, MAPK1) in CLL (16-18).

Hypogammaglobulinemia is a common finding in CLL, and, depending on the disease stage, autoimmune diseases are seen in 25% of patients, (19). Coombs positive autoimmune hemolytic anemia, immune thrombocytopenia, and pure red cell aplasia are among the autoimmune phenomena (20). Along with autoimmune diseases, the production of defective antibodies against certain infections and vaccines may also develop in CLL patients (21). In vitro studies suggest that B-CLL cells may inhibit autologous immunoglobulin production by interacting with CD95 on the surface of normal bone marrow plasma cells (22).

As discussed above, a number of nested and mostly still unexplained immunological mechanisms are among the suspected probable causes of other malignancies in CLL. BCL2 is increased not in CD5 positive normal B cells, but rather in CD5-positive CLL cells.

Furthermore, the number of lymphocytes from BCL2 lymph nodes is greater than the number of lymphocytes from peripheral blood (23). BCL2 is the only proto-oncogene known to suppress programmed cell death (apoptosis), thus prolonging cell survival (24). B-CLL cells with high levels of BCL2 survive in vitro longer than cells with lower BCL2 levels (25). Although 9% of the cases in the present study were CD5-negative, all patients with a second malignancy were found to be CD5-positive. As discussed above, this is in accordance with the increase in BCL2 in CD5-positive CLL patients. This brings the question to mind of whether it is possible that CD5 positivity carries the risk of additional malignancy for CLL patients. In future studies perhaps the subject of whether CD5 negativity has a protective role in the development of second primary malignancies will be debated.

Conclusion

In conclusion, a second primary malignancy was more frequent in patients with chronic lymphocytic leukemia than in the normal population. The mean age of patients with a second primary malignancy was significantly higher than that of normal CLL patients. Although a second primary malignancy was more frequent in male patients, the difference was not statistically significant. All of the patients with the second primary malignancy were CD5 positive. BCL2 proto-oncogene levels were found as increased in CD5-positive CLL cells, not in normal B cells those were positive for CD5. In vitro studies showed that, B-CLL cells with higher BCL2 levels survive is longer than cells with lower BCL2 levels. Presence of the secondary malignancy except CLL may be related with BCL2 increment as well as CD5 positivity. We need more comprehensive studies to determine the relationship between the presence of BCL2, CD5 positivity and secondary malignancies.

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Ethical issues: All Authors declare that Originality of research/article etc... and ethical approval of research, and responsibilities of research against local ethics commission are under the Authors responsibilities. The study was conducted due to defined rules by the Local Ethics Commission guidelines and audits.

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Examination of clinical and demographic characteristics of 14 cases with frontal fibrosing alopecia

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Abstract

Objective: Frontal fibrosing alopecia (FFA) is a rare type of cicatricial alopecia seen in postmenopausal women characterized with band-type frontal/frontotemporal hair traction and/or significant or complete loss of the eyebrows. We aimed to present the demographic, clinical and laboratory characteristics of female patients diagnosed and followed-up with FFA in our clinic by comparing these with the literature data.

Method: A total of 14 patients who admitted to our outpatient clinic with alopecia on the frontotemporal/frontal hairline and were clinically and/or histopathologically diagnosed with FFA between 2011 and 2016 were evaluated in a retrospective manner. The patients were reviewed in terms of the age of lesion onset, localization, accompanying symptom or disease, and treatment options.

Results: The ages of the patients who were followed-up in our outpatient clinic with FFA were between 52 and 73 (mean 2 years). Eight patients (57%) had total eyebrow loss,. Laboratory tests were in normal limits or negative. Comorbidities included thyroid disease, hypertension and coronary artery disease diabetes mellitus. For treatment, all patients were given systemic, intralesional and topical steroid, and topical minoxidil at various times. Four patients received hydroxychloroquine, 2 patients acitretin, 2 patients Vitamin E, 1 patient itraconazole, and 1 patient topical tacrolimus.

Conclusion: FFA should be considered in middle aged and elderly postmenopausal women presenting with hair loss complaints and were detected to have frontal hairline traction and cicatricial alopecia, and the diagnosis should be supported by biopsy. Thereby, the disease progression may be prevented or delayed with early diagnosis and proper treatment..

Keywords: Cicatricial alopecia, frontal fibrosing alopecia

Introduction

Frontal fibrosing alopecia (FFA) was first identified in 1994 (1). FFA is a presentation characterized by symmetrical, progressive traction on frontotemporal hairline and band-type alopecia, predominantly seen in postmenopausal women and frequently also affecting the eyebrows (1-7). The diagnosis is usually made on a clinical basis. Histopathological examination is supportive in diagnosis (2,5,7). While the pathogenesis is not exactly known, its ever-increasing incidence in recent years indicates possible involvement of environmental factors (4). On the other hand, the fact that FFA is seen in more than one individual in some families suggests genetic factors yet to be discovered (8). To date, however, a complete genetic analysis has not been performed. Frequent occurrence in postmenopausal period and successful treatment with 5-alpha reductase inhibitors suggest that a hormone-induced trigger mechanism and androgenetic factors may also be responsible in pathogenesis (2,3,9).

Despite its well-known clinical presentation, clinical studies regarding its treatment are not adequate (2,6). Case reports and series were reported in local and foreign literature (10-19). Here, we aimed to present the demographic, clinical and laboratory characteristics of female patients diagnosed and followed-up with FFA in our clinic by comparing these with the literature data.

Method

A total of 14 patients who admitted to our outpatient clinic with alopecia on the frontal hairline and were clinically and/or histopathologically diagnosed with FFA between 2011 and 2016 were evaluated in a retrospective manner. Photos were taken and patients gave consent form. The patients were reviewed in terms of the age of lesion onset, localization, accompanying symptom or disease, and treatment response. Clinical and demographic characteristics of

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the patients are shown in Table 1. The data is given as mean, percentage, number.

Results

The ages of the patients who were followed-up in our outpatient clinic with FFA were between 52 and 73 (mean 62 years). The disease duration varied between 6 months and 10 years (2 years). None of the cases had history of known trauma or hear traction.

Comparable clinical characteristics were present in all patients. Symmetrical, band-type traction on the frontal hairline extending to preauricular areas, mild atrophy in the skin, follicles at the hairline margin becoming evident, and perifollicular erythema were detected. While 57% of the patients (8 patients) had total loss of eyebrows, others had partial loss. [Figure1-3]. Eleven patients underwent biopsy. Three patients did not accept biopsy.

One patient had lichen planus pigmentosus on the face supported by biopsy. Skin examination other than the scalp was normal in other patients, mucous membranes and nails were normal in all cases. Punch biopsy was taken from an area containing decreased hair follicles on the frontal region of the scalp from 11 patients.

In histopathological examination, decrease in the number and difference in the sizes of hair follicles, perifollicular inflammation, fibrosis in dermis, and decrease in elastic fibers were detected. The patients were regarded as frontal fibrosing alopecia using clinical and/or histopathological findings.

In the laboratory studies, complete blood count, routine chemistry tests, thyroid functions, C-reactive protein, rheumatoid factor, Anti-dsDNA, Antinuclear Antibody (ANA), hepatitis B and C serology were in normal limits or negative.

Comorbidities included thyroid disease in 4 patients, hypertension and coronary artery disease in 3 patients, DM (diabetes mellitus), Vitamin B12 deficiency and iron deficiency anemia in 2 patients each, and Vitamin D deficiency in 7 patients.

For treatment, all patients were given systemic, intralesional and topical steroid, and topical minoxidil at various times. Four patients received hydroxychloroquine, 2 patients acitretin, 2 patients Vitamin E, 1 patient itraconazole, and 1 patient topical tacrolimus.

Discussion

FFA is a cicatricial alopecia characterized by the destruction of hair follicles (2-4). Its localization is different than LPP (lichen planopilaris). Presence of band-type cicatricial alopecia on the frontotemporal region of the scalp is typical. As with all our cases, symmetrical and bilateral traction on the frontal and temporal hairline of the patients is explicit. This traction increases even more over time (2,6,7). Traction on the hairline may vary, progresses slowly and spontaneously stop years after onset (6,7,20). The severity of the disease may also be identified by measuring glabellar-frontal distance which is normally 5.9 cm on average (7). Glabellar-frontal distance in FFA patients was reported to be 6.5-12.5 cm on average (7). However, this measurement was not taken in our cases.

96% of the published cases were reported to have paleness in alopecic skin, destruction of follicular orifices, and skin atrophy without clinical induration and sclerosis (1,5,6,20). All our cases had cicatricial alopecia.

FFA is disease of postmenopausal women by 95%, and the mean onset age of the disease is 67 (45-82) (2,3,4). A multi-center study performed by Vano et al., is the study including the largest series with 355 patients on this subject (14). In this study, investigators reported 12 male patients and 40 premenopausal women. Other cases were postmenopausal women. There are also other studies, though low in number, reporting FFA in male cases and premenstrual women (11,21,22). All our cases were female and in postmenopausal period, and their age varied between 58 and 73 (mean 62).

Eyebrow loss and thinning is frequent, and helps to make diagnosis. Thinning or total loss of the eyebrows was reported in 50-95% of the FFA cases (6,12,13,15). Vona et al. stated that eyebrow loss is present in moderate-severe cases (14). In our study, total eyebrow loss was seen in 57% of the cases (8 cases), and others had partial eyebrow involvement.

Eyelash loss in FFA is occasional and may indicate poor prognosis. Investigators reported that these cases require systemic treatment (14,20,23). In some studies, eyelash loss was detected in 3-26% of the cases (12,13). In our study, eyelash loss was present in 14.2% of the cases (2 cases), and these cases progressed rapidly and did not respond the treatment at all.

General thinning or loss of hair of the other body parts, especially axillary region, was detected in 14-26, 37.5% of the cases (6,12,13). Our one cases had loss in all body hair, however, no follicular keratotic papule was present. Other cases had normal distribution of body hair.

In the early stages of the disease, presence of perifollicular inflammatory papule or erythema was reported in 31-73% of the cases on the progression region of the disease (6,13,15). While most cases had perifollicular erythema, only 2 cases (14.2%) had perifollicular hyperkeratosis.

Symptoms such as itching, burning and pain are seen less compared to lichen planopilaris. Itching on FFA area was reported in 3-67% of the cases in the literature (4,6,11,13,15). Itching was present in 21% of the cases (3 cases).

While the ethiopathogenesis of the FFA is not exactly known, the key role is thought be played by T-cell mediated autoimmune reaction against hair follicles (2,3-5,9,16). Another opinion regarding FFA ethiopathogenesis is the effect of androgen hormonal factors.

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Table 1: Clinical and demographic characteristics of the patients

P. No	Age	Sex	Localization site	Symptoms pruritus	D.period	Concomitant Diseases	Biopsy entity	Lab. findings	Treatment
1	64	F	F-temporal +eyebrows	-	10 years	Asthma,HT, Thyroid Diseases	-	Vit D level low	TS,ILS
2	56	F	F-temporal	-	2 years		+		TS, ILS, H
3	67	F	F-temporal +eyebrows	-	3-4 years	Thyroid Diseases	-	Vit D level low	TS, ILS SS, P, H
4	58	F	F-temporal +eyebrows	+pruritus	1 year	HT,DM,	+	-	TS, ILS, H
5	64	F	F-temporal +eyebrows		3-4 years	-	-	Vit D level low	TS, ILS
6	73	F	F-temporal +eyebrows +eyelashs +diffuse alopecia	FH	1year	HT,Thyroid Diseases,CAD,DM	+	-	TS, ILS Etretinat
7	66	F	F-temporal		1,5 years		+		TS ILS P
8	64	F	F-temporal	FH	2 years		+	Vit D level low	TS, ILS, H
9	58	F	F-temporal		6 months		+		TS, ILS
10	58	F	F-temporal +eyebrows		6 months		+		TS, ILS
11	58	F	F-temporal		1 year		+	Vit D level low	TS, İ ILS, SS, vit E
12	72	F	F-temporal +eyebrows+ eyelashs	+pruritus	2 years	Lichen pigmentosus, CAD,HT,			TS, İ ILS Etretinat
13	59	F	F-temporal		1 year	A (iron-vitB12), Colon Ca	+	Ferritin and vit B12 level low	TS,İ ILS,SS, vit D,vit B12
14	52	F	F-temporal +eyebrows	+ pruritus	6 months	Thyroid Diseases,	+	Vit D level low	ILS, TS, SS, vit E
Total 14 FFA	Med age 62	F	14 F-temporal, 8 eyebrows, 2eyelashs,1 diffuse	3 pruritus	Median period 2 years	1 lichen pigmentosus , 6 vit D deficiency, 4 Thyroid diseases, 2DM,4HT, 2Anemia (iron,vit b12)	Three no biyopsi, 11 biyopsi		14 ILS ,TS,SS 4H, 2Etreinat, 1itracanazol No hormontherapy

ILS: Intralesional enjection, TS: Topical steroid, SS: Sistemic Steroid, F-temporal: Frontotemporal, H: Hydroxychloroquine, HT: Hypertension, DM: Diabetes Mellitus, CAD: Coranary Artery Diseases, FH: Foliculer Hyperkeratosis

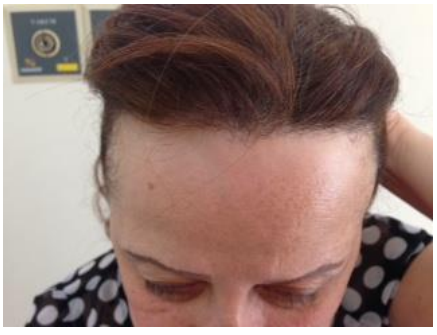

Figure 1 Progressive traction on frontotemporal hairline and band-type alopecia.

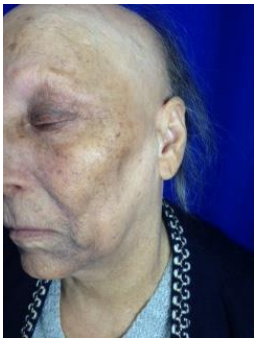

Figure 2: Diffuse hair and eyebrows loss and pigmented lichen planus lesions on the face.

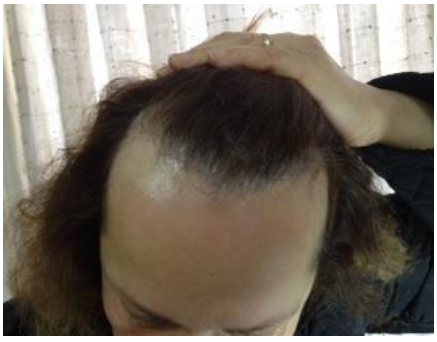

Figure 3: Progressive traction on frontotemporal hairline.

While the facts that it usually affects postmenopausal women, involves frontal scalp, and responds to anti-androgens such as finasteride or dutasteride in some patients suggest this, a significant relationship is yet to be revealed (4,9,24).

Today, FFA is regarded as a clinical variant of LPP which has selectivity for frontotemporal hairline, primarily affects postmenopausal women and is characterized by lymphocytic cicatricial alopecia (2,3,17). Some authors detected lichen planus lesions in patients with FFA (15,19). Furthermore, due to premenstrual female cases with normal levels of sex hormones with accompanying lichen planus lesions, some authors also supported the opinion that the disease is a clinical variant of LPP rather than being an androgen-based disease (11,17). Also, one of our cases had pigmented lichen lesions.

Histopathologically, laminar fibrosis on perifollicular area and fibrosis of the follicular ducts are frequently seen in FFA. No perivascular and periadnexial inflammation is present. These pathological characteristics are common with LPP. The distinctive pathological characteristic of FFA from LPP is that lymphocytic infiltrate and fibrosis of the FFA selectively affect vellus-like follicles on frontal line and muscles. Although not necessarily, perifollicular localized inflammatory lymphocytic infiltrate may be observed on the upper part of the hair follicle (5,23,25).

Mild to moderate follicular inflammation is the common pathological characteristic of female-type hair loss (FMA). However, inflammatory infiltrate in FMA is not limited to isthmus, and perifollicular fibrosis is not a distinctive characteristic as it is in FFA. The specific involvement of intermediate and vellus-like follicles on frontal line and muscles in FFA is yet to be explained (11,13,23,25).

Histopathological examination is necessary to support diagnosis. However, types of primary fibrosing alopecia may not be distinguished histopathologically (6,25). In cases with long-term FFA, the performed biopsies are only reported as cicatricial alopecia, and fibrous tracts without follicle and inflammatory infiltrate are seen (13). Therefore, while some authors show several clinical presentation, they accept FFA as a special variant of lichen planopilaris (5,20). The histopathological examinations of our cases who underwent biopsy could not be distinguished from LPP. Overall, perifollicular fibrosis and lymphoplasmocytic inflammation, and fibrotic bands in dermis were observed. As the histopathological characteristics of our cases could not be distinguished from LPP and the clinical characteristics suggest FFA, we also thought that FFA might be a different variant of lichen planopilaris. However, there is not sufficient data to accept FFA as a separate entity causing lymphocytic cicatricial alopecia (19).

Laboratory tests do not provide the desired assistance in diagnosis (3). Solely, ANA positivity was reported in some cases (14). As a possible autoimmune mechanism plays a role in the pathogenesis, FFA was reported to have the possibility of co-existing with other autoimmune diseases (14). Banka et al. detected co-existence with autoimmune connective tissue disease in 14% of the cases (15). Also, FFA co-existence with autoimmune diseases such as thyroid disease, vitiligo and psoriasis was reported (13,14,15). Some authors were detected to have thyroid pathology and DM in 14-16% of the cases (14,19). We detected thyroid pathology in 28% of our cases. Comorbidities including DM, Vitamin B12 deficiency, Vitamin D deficiency were present in some cases.

Moreover, it was also suggested some medications including angiotensin converting enzyme inhibitors, beta-blockers and thiazides may trigger FFA (14). Ozcan et al. detected history of angiotensin converting enzyme inhibitor or beta-blocker use in 24% of the patients (19). In our study, antihypertensive (angiotensin converting enzyme inhibitor) use was present in four cases (28%) and antidiabetic use in two patients (14%).

The identification of the disease 23 years ago and presence of case and case series around 80 suggest that the diagnosis is usually missed rather than the disease being rare (17,23). The incidence of the disease may be more. It may be due to ignoring and not seeking help in the early stages or the fact that these patients are diagnosed differently (24). Thereby, it causes delay in true diagnosis and treatment, and makes the alopecia permanent. A careful dermatological examination may help to avoid this. Two of our cases were previously diagnosed with alopecia areata and treated accordingly.

In the differential diagnosis of FFA, diseases causing primary cicatricial alopecia including discoid lupus erythematosus, multifocal cicatricial alopecia, follicular degeneration syndrome, traction alopecia, pseudopelade, Graham-Little-Piccardi-Lassueur characterized by diffuse follicular plug or papules, and non-cicatricial alopecia causes including alopecia mucinosa, keratosis follicularis spinulosa decalvans neutrophilic type cicatricial alopecia, alopecia areata, androgenetic alopecia, female-type hair loss, chronic telogen effluvium and familial high hairline should be considered (2,3,6,20).

Very little is known about the natural progression and history of FFA. FFA progresses slowly and the progression stops spontaneously over time, therefore, organizing the treatment and assessing the treatment response may be difficult (2-4). As the alopecia is cicatricial, the aim should be stopping the progression of the disease, preventing more alopecia and decreasing the symptoms (2,26). Also, there is no clear consensus on how to assess the efficacy of FFA treatment. There is no effective option of treatment (3,4,26).

In the literature, preferred treatment options mostly include the use of corticosteroids alone or combined with other medications (26). Steroids may be administered via topical, intralesional or systemic

routes. Oral, intralesional corticosteroid administration was reported to create partial response in 57% of the cases. Most authors considered the steroid treatment as first-line therapy. Intermediate to strong potent topical steroids cannot stop the progression of alopecia in most cases (26). Intralesional steroid administration given in 3-4 weeks intervals was reported to be effective in the early stages of the disease, especially in clinical and histological inflammation stages (3,4). However, as most cases receive combination therapy, the assessment is difficult. Systemic steroid might be effective in rapidly progressing cases with significant inflammatory findings. Hair traction was stopped in approx. half of the cases (42%) using systemic steroid. In some studies, daily administration of oral prednisolone of 25-50 mg in short term was reported to be more beneficial (26). Steroids were found to be less efficacious in FFA than LPP. In our study, we administered firstly intralesional, systemic (intramuscular depot) and topical strong potent steroid treatment to all our cases.

The disease progression stopped, improvement in atrophic skin was observed and a little hair grow was observed in cases who received steroid treatment. While intralesional steroid treatment was found to be successful in 40-97% of the cases with active inflammation in biopsy in the literature, its benefit in cicatricial stage could not be demonstrated (15). We observed slowing down of the progression of the disease with our treatment. We administered intralesional low-dose triamcinolone treatment in patients with eyebrow involvement.

Hydroxychloroquine which is known to be effective LPP is frequently used in FFA. Hydroxychloroquine was demonstrated to considerably decrease the signs and symptoms of the disease and to exert the most effect within the first 6 months (11). Antimalarials stabilize the disease in 30-50% of the patients (7,11,26). We administered hydroxychloroquine treatment as 2x200/day for 6 months in 28% of the cases, however, could not obtain the desired response. Also effective treatment options which are administered in FFA treatment include topical minoxidil, pimecrolimus, tacrolimus, oral acitretin, griseofulvin,doxycycline, mycophenolate mofetil and cyclosporine (4,7,26,28). In our study, we administered acitretin and Vitamin E to 2 cases each, and systemic itraconazole and topical tacrolimus to 1 case each.

In several studies, the most successful medications in FFA were demonstrated to be oral finasteride and dutasteride (12,14,27). However, this effect was also stated to be associated with a possible comorbid androgenetic alopecia. The efficacy of finasteride 2.5 mg use for at least 6 months was demonstrated. In a publication consisting of 111 patients reported in the literature, the most common treatment methods used in FFA patients were reported to be oral finasteride (daily 2.5 mg, for 6-18 months) or dutasteride (daily 0.5 mg for 12 months) (14). Anti-androgenic treatment was demonstrated to be beneficial in 31-47-50% of the cases (27). These agents were often combined with topical minoxidil or intralesional corticosteroids (6, 12,14,15,23,26,27). however, there is still no consensus on how to assess the treatment efficacy in FFA (26).

Conclusion

FFA should be considered in middle aged and elderly postmenopausal women presenting with hair loss complaints and were detected to have frontal hairline traction and cicatricial alopecia, and the diagnosis should be supported by biopsy. FFA may be considered as a special variant of lichen planopilaris. FFA negatively affects the individuals in a psychosocial manner due to progressive and permanent hair loss and decreases the quality of life. Therefore, with proper diagnosis and treatment, the symptoms may be eased and the disease progression may be prevented in most of the patients. In our case series of 14 patients who were diagnosed clinically and histopathologically, general information regarding FFA which is a lesser known cause of cicatricial alopecia was given, its demographic and clinical characteristics, and treatment options were reviewed, and comparison was made to general literature. The limitations of our study include being retrospective, low number of cases, and not being able to observe the true efficacy as we could not administer anti-androgen treatment.

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Ethical issues: All Authors declare that Originality of research/article etc... and ethical approval of research, and responsibilities of research against local ethics commission are under the Authors responsibilities. The study was conducted due to defined rules by the Local Ethics Commission guidelines and audits.

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