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Thyroid Cancer in Patients with Rheumatic Diseases

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Research Article

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Abstract

Summary: A close bidirectional relationship coexists in patients with malignancies diseases and rheumatic diseases (RD). The autoimmune thyroid disease and RD go beyond the multifactorial causes of malignant development. Different autoimmune elements produced by thyroid cancer are detected in SEL and RA patients. Autoantibodies against the thyroid gland are also detected in patients with RD. The objectives of this study are to know the clinical behavior of both entities and to describe the clinical characteristics of the patients with rheumatic diseases and thyroid cancer concurrent.

Methods: This is a descriptive study with a serie of cases and reviews of literature. The records of patients with diagnosis of thyroid cancer and rheumatic disease according to American Rheumatology Collage were reviewed during the study period. The risk factor, clinical characteristics of the patients and histological subtype of thyroid cancer were classified according to world health organizations (WHO) using AGES-stage system. The thyroid cancer staging was done according to the American Joint Committee on Cancer (AJCC) and therapeutic approached. The univariable review was realized with frequency and percentage using excel program 2010. The laboratory test was processed using operative laboratory system ClinSis 2015.

Results: The records of 250 patients with thyroid cancer diagnosed, 5 with rheumatic diseases, represent 2%. Female 4 (80%) 1 man (20%). 3 Systemic Erythematous Lupus (SEL) (60%) and 2 Rheumatoid arthritis (RA) (40%) 1 patient with both. The age range was 22-48 years old, the average age was 33 years old. Serologic test to SEL reveled: Antinuclear antibodies (ANA-iFi) positive in all cases and the patients with RA: Rheumatic Factor positive 100%. SEL patients presented hematologic and cardiovascular symptoms in all cases and one case with chronic failure kidney, with successful kidney transplant during two years and then required hemodialysis.The echocardiogram reported pulmonary hypertension, mitral and tricuspid valves insufficiency and 1 patient with severe tricuspid valves insufficiency plus right heart dilatation. One case with left hip severe osteoarthritis that required hip replacement. There was another patient with incidental finding: pleural effusion, ascitis and hepatomegaly. The patient with both disease died by severe pulmonary hypertension. Rheumatoid arthritis was diagnosed in 2 patients (40%) 1 man and 1 female. 1 patient with symmetric polyarthritis, morning stiffness and joint limitation, affecting elbow and carpus. The other presented polyarthritis compromising both hands and cervical spine, who developed left lower limb edema with Doppler report of proximal pseudoaneurysm. The classic papillary carcinoma was diagnosed in the majority of cases, and it was classified as low risk in patients with SEL and patients with intermediate risk were RA patients. The thyroid cancer staging was: staging I corresponded to SEL and staging IV corresponded to RA. The surgical approach was two patients with total thyroidectomy and one with right lobectomy in SEL. Two total thyroidectomy plus modified radical neck dissection corresponded to RA patients due to extra capsular extension and nodal positive. These used radio ablation with Iodo.

Conclusion: The rheumatic diseases (SEL and RA) concurrent in patients with thyroid cancer, were presented in the minority of cases in our little serie. The young woman was the most affected. Most of the cases presented hematologic symptoms and a

severe case with Rhupus syndrome that die for pulmonary complication. The patients with classic papillary thyroid cancer in early stage (low risk) were treated with total thyroidectomy plus radio iodine ablation in the majority of the cases without complications. Our result is similar as the international literature.

Keywords: Malignancies Diseases; Rheumatic Diseases; Autoimmune Thyroid Disease; Thyroid Cancer; Rhupus Syndrome

Abbreviations: RD: Rheumatic Diseases; AJCC: American Joint Committee on Cancer; WHO: World Health Organization; SEL: Systemic Erythematous Lupus; RA: Rheumatoid Arthritis; ANA: Antinuclear Antibodies; RAI: Radio Ablation Iodine; AID: Autoimmune Disease; ATD: Autoimmune Thyroid Disease; HT: Hashimoto's Thyroiditis; PTC: Papillary Thyroid Cancer; FNA: Fine Needle Aspiration; MAPK: Mitogen-Activated Protein Kinase; RIA: Radio Iodine Ablation.

Introduction

Several chapters have been written about cancer with autoimmunity and show a bidirectional relationship. Patients with malignancies diseases may develop rheumatic manifestation [1]. Autoantibodie activity has been identified in patients with solid tumors and hematological malignancies also anty-oncoprotein antibodies, anti-tumor suppressor genes, antiproliferation associated antigens, to name a few [2-4]. Antinuclear antibodies are detected in patients with cancer (Anti-DNA, Anti- phospholipid autoantibodies), 2-12% of these patients have lupus anticoagulation activity. These autoantibodies are called Natural autoantibodies [5,6].

The activation of autoimmune mechanisms among patients with cancer may be associated with development of rheumatic diseases (RD). On the other hand, several studies in patients with RD has demonstrated the increased risk to develop cancer, compared with general population [7,8]. Various RD have strong association with benign thyroid disorders (Hashimoto's and Grave diseases, thyroid acropacy) due to influence of several risk factor: genetic and environment, iodine intake, chronic infection diseases, that at the end, develop a really autoimmune systemic reaction [9]. The objectives ares to know the clinical behavior of both entity and to describe the clinical characteristics of the patients with rheumatic diseases and thyroid cancer concurrent.

Methods

This is a descriptive study with a serie of cases and reviews of literature. The records of patients with diagnosis of thyroid cancer and rheumatic disease according to American Rheumatology Collage were reviewed during the study period [10]. The risk factor, clinical characteristics of the patients and histological subtype of thyroid cancer were classified according to world health organizations (WHO) and AGES-stage system [11,12]. The thyroid cancer staging was done according to the American Joint Committee on Cancer (AJCC) and therapeutic approached [13]. The univariable review was realized with frequency and percentage using excel program 2010. The laboratory test was processed using operative laboratory system ClinSis 2015.

Results

The file a record of 250 patients with thyroid cancer diagnosed was reviewed, 5 patients with rheumatic diseases, represent 2%, female 4 (80%) 1 man (20%). The age range was 22-48 years old, the average age was 33 years old (Figure 1).

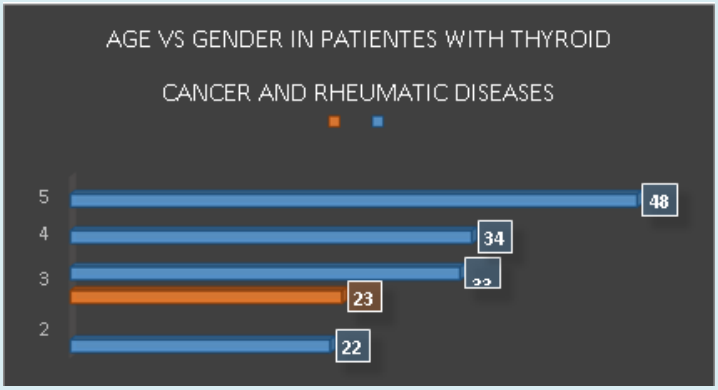

Figure 1: Age Vs Gender in Patients with Thyroid Cancer and Rheumatic Diseases.

The rheumatic diseases diagnosed were 3 Systemic Erythematous Lupus (SEL) (60%) and 2 Rheumatoid arthritis (RA) (40%) 1 patient with both diseases. The clinical presentation to SEL, were hematologic symptoms the 3 patients (Figures 2-4), 1 patient with high blood pressure, chronic failure kidney and hemodialysis therapy for 2 years, she had successful kidney transplant for two years and then required hemodialysis therapy.

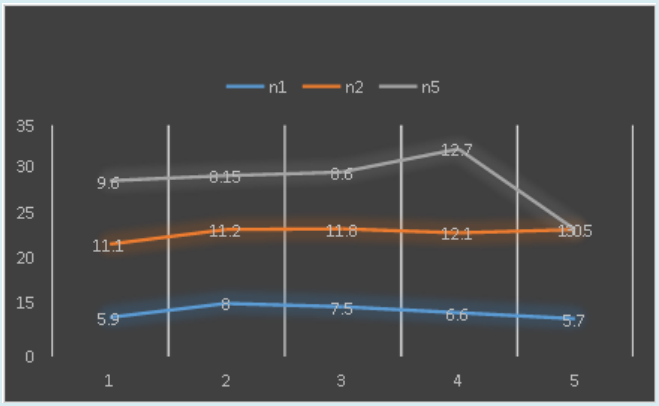

Figure 2: Hemoglobin gr/dl in patients with thyroid cancer and SEL.

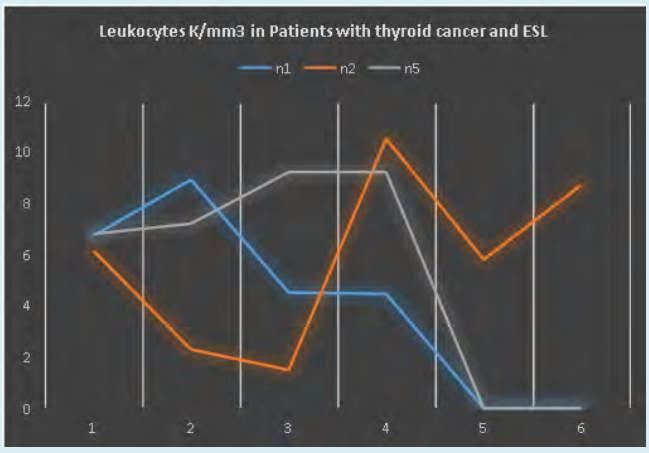

Figure 3: Leukocytes K/mm3 in Patients with thyroid cancer and SEL.

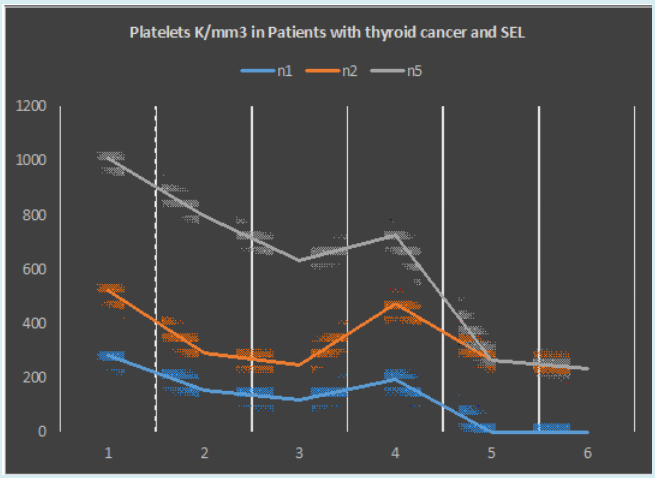

Figure 4: Platelets K/mm3 in Patients with thyroid cancer and SEL.

Serologic test to SEL reveled: Antinuclear antibodies (ANA-iFi) positive in 3 cases (100%), Anti-Cal antibodies positive 1 Patient (33.3%), Rheumatoid factor positive 1 patient that presented both diseases. 2 patients (66%) the echocardiogram reported pulmonary hypertension (33mmHg/ 50mmHg), mitral and tricuspid valves insufficiency 1 patient (33.3%) and 1 patient with severe tricuspid valves insufficiency plus right heart dilatation. Only 1 patient with normal echocardiogram.

Imagine finding TC reported left hip severe osteoarthritis, required hip replacements, the patients with both diseases; 1 patient with 10th costal fractured as incidental finding plus pleural effusion, ascites and hepatomegaly. The 3 patients (100%) were treated with Plaquinol and 1 case with Metrotexate. The patient with both disease died by severe pulmonary hypertension. Rheumatoid arthritis was diagnosed 2 patients (40%), 1 man and 1 female, 1 patient with symmetric polyarthritis , morning stiffness and joint limitation, affecting elbow and carpus; the other presented polyarthritis compromise both hands and cervical spine, after developed left lower limb edema with Doppler report of proximal pseudoaneurysm.

Serologic test to RA were Rheumatic Factor positive 2 patients, (100%), Citrullinated cyclic peptide antibodies and PC Reactive positive 1 patient. 1 patient developed left sub deltoid bursitis diagnosed by ultrasound. The hematologic test was normal in both patients. Both were treated with Plaquinol and Metrotexate. The Papillary carcinoma classic was diagnosed in 4 patients (80%), 1 patients (20%) with Follicular variant of Papillary carcinoma corresponded to the man patient. The risk factor classification using AGES stage system was: 3 patients diagnosed with SEL were low risk (60%) and 2 patients with intermediate risk were RA patients (40%).

The thyroid cancer staging was: 3 patients with clinical staging I corresponded to SEL (60%) and 2 patients with clinical staging IV corresponded to RA (40%). The right lobe was affected in 4 patients (80%) and 1 in the left lobe of the thyroid (20%). The surgical approached was 2 patients with Total thyroidectomy and 1 with right lobectomy in SEL. 2 Total thyroidectomy plus modified radical neck dissection corresponded to RA patients (40%). Surgical pathologic reported: 2 Papillary microcarcinoma less than 10mm and 1 measured 15mm, 1 Hashimoto Thyroiditis concomitants with cancer and 1 multifocally carcinoma. 1 papillary microcarcinoma and 1 measured less than 20mm in RA patients. 2 extra thyroid extensions were reported: extra capsular extension and neck nodal positive in patients with RA. 4 patients used Radio ablation iodine (RAI) therapy (80%), 2 ESL and 2 RA patients. The report of Antithyroglobulyn antibodies range was 15, 9-778, 5. 1 patient with RA with high level prior and post-surgery. Without evidence of disease post-surgery, the rest were normal (Figure 5).

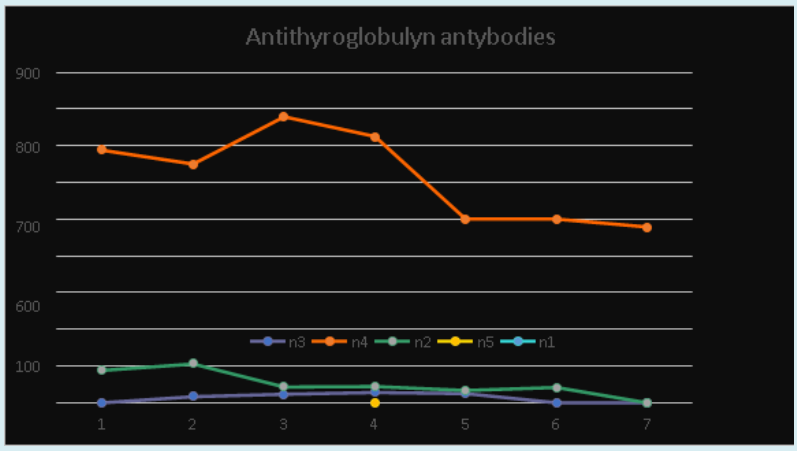

Figure 5: Antithyroglobulyn antibodies.

Discussion

The thyroid cancer is the most common between the endocrine tumors. Nowadays the diagnosed in early stage is due to use of high technology ultrasound in the clinical practice. Those have been reflected in several researches with an increase incidence in the last decade [14-16]. The coexistence among malignant neoplasm and autoimmune disease (AID) has been demonstrated; a particular group is the Systemic Erythematous Lupus (SEL) patients, the range of 0.4-3.4% the thyroid cancer was found in this people group as our results [17]. The autoimmune thyroid disease (ATD)

as Hashimoto's thyroiditis (HT)or Graves Basedow disease could be a clinical manifestation of AID (ESL or Rheumatic Arthritis) [9,18].

One of our patients treated by papillary thyroid cancer (PTC) development LES two years later; we reviewed the first Fine Needle aspiration (FNA) the report was Hashimoto Thyroiditis and follow up a new FNA reported the thyroid cancer. This topic was described by Biro same as our patient. The period of time of duration of diagnosed of SEL when cancer, the range was 2-30 years [19]. The 62% of patients with ATD have someone RD. The 51 % of patients with SEL have antibodies anti thyroid compared with control (p:<0.05) [20-23]. The first proposed about the relationship among AID and malignancies neoplasm was by Virchow and after several papers published different aspect about this topic [24-27]. The relationship among gender and age, have been established in both entities, ours results are similar as international literature. It is currently know that increasing age and female gender are associated with increasing risk of developing autoimmune disorders [28,29]. The close relationship of ATD and RD go too far in the heterogeneity to development malignant neoplasms. Different paper reported the increase risk of cancer in patients with SEL. Lewis, et al. reported an increased risk of malignity in 484 patients with SEL [8,30].

Lymphomas and Soft tissue Sarcoma are more common in SEL than general population. Petterson series reported 12 female patients with thyroid cancer. However, other authors did not find this relation [8,31]. In our serie of cases there are 3 female patients with SEL and thyroid cancer, as reported by Petterson. Different autoimmune elements produced by thyroid cancer are detected in SEL and RA patients, this clearly show coexist autoantibodies against the thyroid gland in patients with RD [32]. The patients with SEL have functional disorder in humoral and cellular immunity system. In thyroiditis, especially HT, parenchyma of thyroid gland is progressively lost and replaced by cells of the inflammatory infiltrate. The persistent stimulation of residual thyrocytes with such molecules could induce the activation of NF-β in follicular cells, thereby creating a functional network between thyroid epithelial cells and inflammatory cells [33].

This cytological alterations and nuclear modifications are similar to those of papillary carcinomas, suggesting that both neoplastic and autoimmune diseases could share the same molecular pathogenesis [34]. The mitogen-activated protein kinase (MAPK) signaling pathway is a foremost event in the carcinogenesis of the most common endocrine malignancy, the papillary thyroid carcinoma (PTC). Affected elements include RET/PTC re-arrangements and point mutations of the RAS and BRAF genes. Mutations in these genes are found in over 70% of PTC [35,36]. Other concurrent factor detected in patients with AD is several viral infections that could contribute to development thyroid cancer, such as Hepatitis C infection. These patients have high levels of serum anti-thyroperoxidase and/or anti- thyroglobulin autoantibodies. Hepatitis C chronic infection shows a higher prevalence of papillary thyroid cancer than controls, in particular in patients with autoimmune thyroiditis [37].

Clinical presentation of the patients with SEL was hematologic symptoms, anemia, leucopenia and platelets diseases. Hematological complications are frequent in SEL and are considered as good prognosis compared to other organs involvement. Miranda reported thrombocytopenia (severe in 62%), it was the most common hematological feature followed by hemolytic anemia (severe in 37%) and neutropenia (severe in 89%) [38,39]. On the other hand, the level serum antibodies thyroid in ours patients did not present a relevant change. Is precise to remember that less of 25 % patients with thyroid cancer have antibodies thyroid positive, and 10 % are present in normal population [40,41]. One patient with thyroid cancer and both RD (SLE and RA). This clinical manifestation is called Rhupus syndrome or overlap syndrome between RA and SEL. However, this syndrome is still in debate, some consider as different entity and others as aggressive presentation of SLE, with bad prognosis same as our dead patient [42,43]. Rubini analyzed clinical and serological data of 176 patients with diagnosis of Rhupus, derived from a total of 16 studies. A strong heterogeneity in the elements taken into account to establish the presence of Rhupus, reflecting the lack of consensus and validated criteria to define the disease [44,45]. SEL affect several organ, the kidney appears to be one of the most common, and at the same time, more serious complication. The prevalence of renal disease ranged from 29 to 75%. The patients with lupus nephritis, despite treatment, 10-15% go into end stage renal failure [46,47].

The recurrent lupus nephritis is common in patients with kidney transplant, those with major prevalence in case when was associated with a receiving kidney from living donor, as our patient [48]. On the other hand, the lung manifestation occur most commonly in SEL patients: pleural effusion 58%, as our results and a severe case of bilateral effusion 50% [49,50]. The pulmonary hypertension occurs in 25% patients with SEL due to interstitial diseases, recurrent embolism and vasculitis. This is a bad prognosis because they develop pulmonary and heart failure same as our case [51]. The cardiac compromise is frequent in SEL patients, as ours cases; the first report was realized by Osler in 1895. The prevalence is variable; the range could be major 50%. The lupus can affect several cardiac structure (pericardium, myocardium and endocardium, valves, conduction tissue and coronary artery) [52,53].

The bone fracture has several factors in the pathogenesis of the SEL; bone resorption is secondary to vasculitis and decrease of bone matrix secondary to use steroid therapy in the patients. Femoral head is the most affected 5-50 % reported by Resnick. Ours patients with Rhupus Syndrome received a hip replacement [54,55]. The patients with RA have similar risk to develop cancer as SEL, but, still is controversial topic. Jianguang Ji, reported that RA had worse prognosis for all and many site specific cancer compared with patients without RA. Their series reported 64 patients with thyroid cancer, almost all older patients, different as our result [56,57]. However, Hemminki, et al. [58] only found few cases of thyroid cancer related to RA, their series present major number case of lymphomas and squamous cell skin cancer.

Almost all of patients showed morning stiffness as reported by Ndongo S, et al. [59]. In the large overlapping field of infections and rheumatology, many autoimmune diseases may present as fever of unknown origin, and, on the other hand, many different infectious agents cause signs and symptoms mimicking a systemic autoimmune disease. Clinical manifestations affecting the skin and its annexes, oral cavity, joints, and periarticular structures and also major organs such as the heart and vascular system, lung, liver, spleen, and gastrointestinal tract can be initial symptoms of a systemic autoimmune disease. The good knowledge of underlying pathogenetic mechanisms of particular clinical manifestations, the through physical examination, and the accurate use and interpretation of laboratory, serological, and imaging findings are necessary skills in overcoming the challenging differential diagnosis [60].

The most frequent comorbidity reported by Rajaine was dyslipidemia (43.5%) followed by hypertension, as one of ours cases (37, 9%) and thyroid cancer the malignancy tumors most frequent in RA patients [61,62]. The Rheumatoid factor is positive in ours patients as other paper 93% [63]. However, other paper reported low level of rheumatoid factor positive as in Angelotti study (65.5% of cases) [64]. The majority of ours patients with thyroid cancers are classic papillary. One case with previous HT similar as other paper. This has been a topic of discussion as other aspect of autoimmune diseases such as the rheumatic diseases [65,66]. The question of How thyroid malignancies develop despite immune responses, or does disorder thyroiditis develop because of an antitumor immune response, or if the neoplasm arose from previous chronic inflammation [67].

Within this controversy, it is important to be clear about the role of cellular and humoral immunity [68,69]. Ferrari reported cancer onset can be associated to the extended and serious immune stimulus linked to the autoimmune disease and paraneoplastic autoimmune diseases characterized by rheumatic manifestation that can occur before, contemporaneously or after the onset of the tumors [70]. Almost all the patients diagnosed in early stage and classified as Low Risk detected during the follow up for their rheumatic diseases. The standard treatment was total thyroidectomy plus I-131 ablation by positive nodal and capsular invasion. Total thyroidectomy as the primary initial surgical treatment option for nearly all differentiated thyroid cancer >1cm with or without evidence of loco-regional or distant metastases. The requirement for routine use of radio Iodine ablation (RIA) was one of the major reasons given in support of total thyroidectomy in low to intermediate risk patients, our current more selective approach to RAI ablation [71].

Only one case with right lobectomy, the case of SEL plus chronic failure kidney was a conservative consideration to reduce the risk of other complication. Often lobectomy was done based on proper selection of low to intermediate risk patients considering comorbidity conditions [72-74].

Conclusion

The rheumatic diseases (SEL and RA) concurrent in patients with thyroid cancer, were presented in the minority of cases in our little serie. The young woman was the most affected, the majority with Hematologic symptoms, there was a severe case with Rhupus syndrome that die for pulmonary complication. The patients with classic papillary thyroid cancer in early stage (low risk) were treated with total thyroidectomy plus radio iodine ablation in the majority of the cases without complications. Our results are similar as the international literature.

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