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RESEARCH ARTICLE

CLINICAL CASE VIRAGE LYMPHOMATEUX AU COURS DU SYNDROME DE GOUGEROT SJOGREN MIMANT UN CANCER DU SEIN : A PROPOS D'UN CAS

LYMPHOMATOUS TURN DURING GOUGEROT SJOGREN SYNDROME MIMICKING BREAST CANCER: A CASE REPORT

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Abstract

Gougerot sjogren syndrome is a mild, slowly progressive autoimmune disease associated with low morbidity and mortality, characterized primarily by organ-specific autoimmune manifestations and systemic manifestations. Indeed, these complications, feared during the evolution, have been known and reported for many years. This risk of non-hodgkin lymphoma is, moreover, notably greater during primary Gougerot sjogren syndrome than during any other autoimmune pathology. The most commonly affected tissue is the exocrine salivary glands, but other tissues may be involved: stomach, nasopharynx, skin, liver, kidney, lung, breast. In both models, primary Sjögren's syndrome non-Hodgkin's lymphoma or chronic viral hepatitis infection, autoreactive B lymphocytes with rheumatoid factor activity continuously stimulated by the autoimmune process are particularly exposed to clonal transformation by a second oncogenic event.

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Introduction:-

Gougerot-Sjögren syndrome (SGS) is an autoimmune disease characterized by lymphocyte infiltration of the salivary and lacrimal glands, leading to progressive destruction of glandular tissue, and the production of autoantibodies. The occurrence of non-Hodgkin lymphoma (NHL) is a known and feared complication in the course of this condition, which is more common than in other autoimmune or chronic inflammatory conditions. Most of these lymphomas are low grade, but can be of different histologic types. The relative risk of developing NHL ranges from 6.1 to 44.4 depending on the study. We discuss the pathophysiological mechanisms underlying the occurrence of NHL during primary SGS as well as Particularities of lymphoma change during SGS viral hepatitis + (VHC).

Case description

This is Mrs. YARRA Zohra, 89 years old widowed mother of a child, hypertensive for 10 years, known VHC + since 2010 with hepatic fibrosis and moreover followed in internal medicine for primary Gougerot Sjögren syndrome since 2007 considered stable without treatment . Surgically, the patient is operated on for a fractured humerus 6 months after her hospitalization.

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The patient presented for consultation for inflammation of the left breast which had progressed for 2 months with the autopalpation of a nodule in the same breast without associated nipple discharge, all of which progressed in a context of preservation of the general condition.

The initial examination found a patient in fairly good general condition with normal tension at 130/80mmHg, eupneic 80 c/min, body mass index (BMI) at 22 kg / m².

Examination of the breasts found at the level of the left breast: A large inflammatory breast with orange peel sign at the lower quadrants hot painful on palpation with the presence of a 4x4 cm nodule, at the level of the mobile ipsilateral axillary extension in relation to both deep and superficial planes without discharge or nipple retraction nipple (fig1; 2).

Examination of the right breast does not find any abnormalities.

At the level of the left supraclavicular area, there is the presence of a mobile centimetric lymphadenopathy on both planes.

The breast assessment shows on mammography:

Left:

Marked thickening of the skin covering diffuse lymphomatous overdensity.

Right:

Less marked diffuse thickening of the lymphedematous type skin coating.

Bilateral breast ultrasound showed:

Left:

Hyperechoic infiltration of the left breast with galactophoric ectasia + diffuse lymphedema with the presence of a heterogeneous polylobed hypoechoic lesion towards the axillary extension, measuring 30x18 mm. Associated with a hypoechoic dedifferentiated satellite lymphadenopathy of 11 mm.

Right:

Galactophoric ectasia and moderate diffuse subcutaneous lymphedema without circumscribed lesion, we note the presence of a centimetric lymphadenopathy ipsilateral satellite.

Ultimately, the ultrasound mammographic examination was rated ACR BIRADS 5 on the left and BIRADS 4 on the right.

A TRU-CUT biopsy was performed on the nodule of the axillary prolongation, concluding in a histological appearance in favor of an inflammatory, intense, chronic suppurative change with necrosis of the mammary parenchyma. No obvious sign of malignancy or specific inflammation.

The patient in front of this picture underwent a surgical biopsy associated with a lumpectomy of the left breast.

The anatomopathological examination of the operative parts was concluded.

At the level of breast biopsy in the presence of an atypical polymorphic cell infiltrate, the immunohistochemical study of which is in favor of lymphomatous proliferation.

At the lumpectomy patch to a chronic non-specific fibro-inflammatory rearrangement. No sign of malignancy.

Discussion:-

Primary Gougerot-Sjögren syndrome (SGS) is an autoimmune disease characterized by progressive destruction of the exocrine glands leading to disabling symptoms such as xerostomia, xerophthalmia and vaginal dryness. This relatively common condition (from 0, 02 to 4% of the population, depending on the diagnostic criteria used) is due to global lymphocytic infiltration of the affected glands, associated with chronic B lymphocyte activation. This B activation, responsible for the presence of serum markers sometimes associated with the disease (anti-Ro / SSA,

anti-La / SSB autoantibodies, rheumatoid factor, cryoglobulinemia and / or hyper-gammaglobulinemia), also constitutes a risk factor for the development of non-Hodgkin lymphoma.

Primary Sjögren's syndrome is the autoimmune disease associated with the greatest risk of lymphoma. It is an autoimmune epithelitis characterized by the presence of a glandular lymphocytic infiltrate, primarily salivary.

This risk of NHL is also significantly greater during primary SGS than during another autoimmune pathology such as systemic lupus erythematosus or rheumatoid arthritis. Thus, a meta-analysis published in 2005 reports a standardized incidence ratio (RSI), comparing the incidence rate of NHL in a specific population to that expected in the general population, estimated at 18.9 during the evolution of SGS, to 7.5 in systemic lupus erythematosus and to 3.2 in rheumatoid arthritis [1].

The first publications identifying the risk of developing NHL during SGS date back to 1964 [2]. This complication was confirmed a few years later, in 1978, by Kassan et al., who reported a 44.4-fold risk of presenting NHL during the course of the disease compared to the general population [3].

This risk was revised downwards in the early 2000s, with the publication of a Finnish study in 2001 which reported, in a cohort of 110 patients with primary SGS, the occurrence of three cases of NHL, corresponding at a standardized incidence ratio of 13 [4]. In 2006, in a Swedish study, based on the study of Swedish health registries, the relative risk of developing lymphoma was estimated at 16 in patients with SGS defined by the American-European classification criteria [5].

More recently, a meta-analysis (12 case-control studies, almost 30,000 cases) aiming to establish an association between NHL and autoimmune diseases found an overall risk of NHL multiplied by 6.5 during SGS, finally forming part of the lowest published risks [6].

The clinicohistological picture is fairly homogeneous. The majority of lymphomas complicating primary Sjögren's syndrome are lymphomas of the marginal zone and in particular lymphomas of the lymphoid tissue associated with the mucous membranes (mucosa-associated lymphoid tissue [MALT]) [7]. The first frequency localization is involvement of the salivary glands, target organs of autoimmune disease. The second histologic type by frequency is diffuse large-cell B lymphoma, which may be the result of transformation into low-grade lymphoma. In addition, in our patient, the lymphomatous localization seems to affect the mammary gland first, mimicking until the moment of histological confirmation the appearance of classic mammary tumor involvement. Cases certainly described in the literature but remain quite rare.

During SGS, focal lymphocyte infiltration is overwhelmingly T-type CD4 +. The progression to malignant B cell proliferation from this inflammatory infiltrate is complex and occurs in several stages.

The final step in the process is the transition from benign B cell proliferation to malignant expansion. This expansion is the result of various genetic alterations and translocations in the loci of genes of immunoglobulins, proto-oncogenes and other genes involved in the regulation of the cell cycle. Two chromosomal translocations involving the MALT1 genes, the t (8; 9) (q21; 21) translocation on the one hand and the (10, 11) (q32; q21) translocation on the other, were considered to be events. specific genetics during lymphomagenesis of MALT-type lymphomas. However, these translocations were only found in 27% and 15%, respectively, of patients with MALT lymphoma complicating SGS [12].

At the same time, new mutations in the tumor suppressor gene p53 have been detected in two out of five patients with low-grade NHL, suggesting the role of this gene in lymphomagenesis during SGS [13].

However, the involvement of specific molecular abnormalities in lymphomagenesis during SGS has not been fully demonstrated. The role of a specific immunological process during SGS as well as the characteristics of the local glandular microenvironment leading to B-cell proliferation have been raised. Streubel B et al in their study investigating the frequency of chromosomal aberrations involving MALT1 in lymphoma patients with Sjögren syndrome. The [10, 11] (q21; 21) translocation is in fact only detected in one in 17 (6%) patients with SGS with extradigestive NHL, compared with six in nine patients (67%) with SGS and gastric-localized NHL, suggesting the role of potential pathogenic factors within the salivary gland. The frequency of the rearrangement of the MALT1

gene therefore appears to be relatively low in the population of patients with SGS complicated by NHL, of extradigestive localization, but relatively high in patients with SGS and gastric NHL, at least partially explaining the poor response of these forms of NHL to eradication of *H. pylori* [14].

Another actor playing a role in SGS lymphomagenesis is the cytokine BAFF (B cell activating factor belonging to the TNF family), cytokine belonging to members of the TNF receptor family, involved in the induction and perpetuation of activation and proliferation of B lymphocytes [15]. This cytokine is excessively produced in several autoimmune diseases, but particularly in SGS, correlated with autoantibody titers [16]. This cytokine is expressed within the salivary glands, particularly by glandular epithelial cells and T lymphocytes. Its serum level is also correlated with the degree of focal lymphocyte infiltration within the accessory salivary glands and with the formation of germinal centers [17].

BAFF is involved in the survival of malignant B cells, and BAFF production correlates with histological grade and patient survival in a study of patients with NHL [18]. These observations make this cytokine an important candidate in lymphomagenesis during SGS. It is also a very interesting therapeutic target, currently evaluated in at least two phase II therapeutic trials testing an anti-BAFF human monoclonal antibody, belimumab, during primary SGS.

The onset of lymphoma following SGS associated with HCV + as in the patient subject to our description is the subject of particular interest in the scientific literature.

In fact, lymphomas complicating primary Sjögren's syndrome and chronic HCV infection share a large number of characteristics: predominance of low-grade non-Hodgkin B lymphomas, lymphoma-type histology of the marginal zone, localization to target organs of the disease, possibility of transformation into diffuse large B-cell lymphoma and association with cryoglobulin (monoclonal or polyclonal immunoglobulins [Ig] M with rheumatoid factor activity and cryoprecipitates) [19]. This homogeneity of the clinicobiological picture suggests a common pathophysiology with a central role of chronic antigenic stimulation by immune complexes stimulating B lymphocytes with rheumatoid factor activity.

Chronic HCV infection is characterized by the chronic and massive presence of immune complexes made up of anti-HCV antibodies and viral peptides. In primary Sjögren syndrome, immune complexes consist of SSA or SSB or other autoantigens / anti-SSA, anti-SSB or other autoantibodies. These immune complexes are highly immunogenic and stimulate B lymphocytes secreting IgM with anti-IgG (rheumatoid factor) activity [20]. The progression towards lymphomatous proliferation of these B lymphocytes with rheumatoid factor activity is thought to result from the accumulation of mutations and / or chromosomal abnormalities facilitated by chronic antigen stimulation or by a deficit in proliferation control. Cryoglobulin is the first step in this process, lymphoma is the second.

In both models, primary Sjögren's syndrome non-Hodgkin's lymphoma or chronic HCV infection, autoreactive B lymphocytes with rheumatoid factor activity continuously stimulated by the autoimmune process are particularly exposed to clonal transformation. by a second oncogenic event.

Thus, lymphomas complicating primary Sjögren's syndrome represent the ultimate stage of chronic antigenic stimulation of the B lymphocyte. They are the result of this runaway of the adaptive immune response associated with the loss of control mechanisms.

The overall five-year survival rate of patients with MALT-type lymphoma is, depending on the series, from 85 to 95%, subject to some variations depending on the site [16]. In MALT lymphomas in general, however, the ten-year survival rate is greater than 75% [16]. The prognosis for this type of NHL is influenced by prognostic factors for NHL in general, including clinical signs of scalability, large tumor mass, elevated LDH levels, beta 2 microglobulinemia, low albumin. The presence of a contingent of large cells at diagnosis is also an element of poor prognosis [17].

Concerning the therapeutic management of this type of NHL, the data in the literature are poor. An interesting retrospective study notes the absence of a significant difference, in terms of survival, of patients with salivary-located MALT-type NHL treated by different modalities (chemotherapy, radiotherapy, surgery) compared to the same type of untreated patients [18]. Likewise, in 1999, a Greek study reported an uncomplicated course in the absence of treatment in patients with a low-grade localized form of salivary NHL, with a median survival of 6.4

years confirming the little interest in indicating a therapy in low-grade, localized forms of NHL confined to the exocrine glands [19].

On the other hand, in the case of low-grade multi-nodal lymphomatous involvement, it is justified to propose therapeutic management. These are alkylating agents (chlorambucil or cyclophosphamide) and purine analogues, resulting in complete remission rates of around 75% [20]. Rituximab, a chimeric monoclonal antibody targeting the CD20 molecule of the B lymphocyte surface, has hitherto justified its place in the treatment of visceral impairment of SGS. This molecule has been used either as monotherapy or in combination with other cytotoxic agents. Finally, the response rate to rituximab (used alone or in combination) is approximately 77%. For example, the more aggressive forms of NHL (transformed MALT lymphomas, or de novo large cell lymphoma) should be treated with multidrug therapy, including rituximab.

Conclusion:-

Non-Hodgki- lymphoma of primary Sjögren syndrome or chronic infection with HCV, autoreactive B lymphocytes with rheumatoid continuously stimulated by the autoimmune process are particularly exposed to clonal transformation by a second oncogenic event. Thus, lymphomas complicating Sjögren syndrome primitive represent the final stage of antigenic stimulation chronic B lymphocyte. They are the result of this racing of the adaptive immune response associated with the loss of control mechanisms. Continued progress in understanding of the precise mechanism of appearance of these lymphomas will allow progress both in the area of autoimmunity and oncohematology.



Figure1:- At the left breast: A large inflammatory breast with orange peel sign at the lower quadrants.



Figure 2:- Nodule of a 4x4 cm at the level of the mobile left axillary extension in relation to both deep and superficial planes without discharge or nipple retraction nipple.

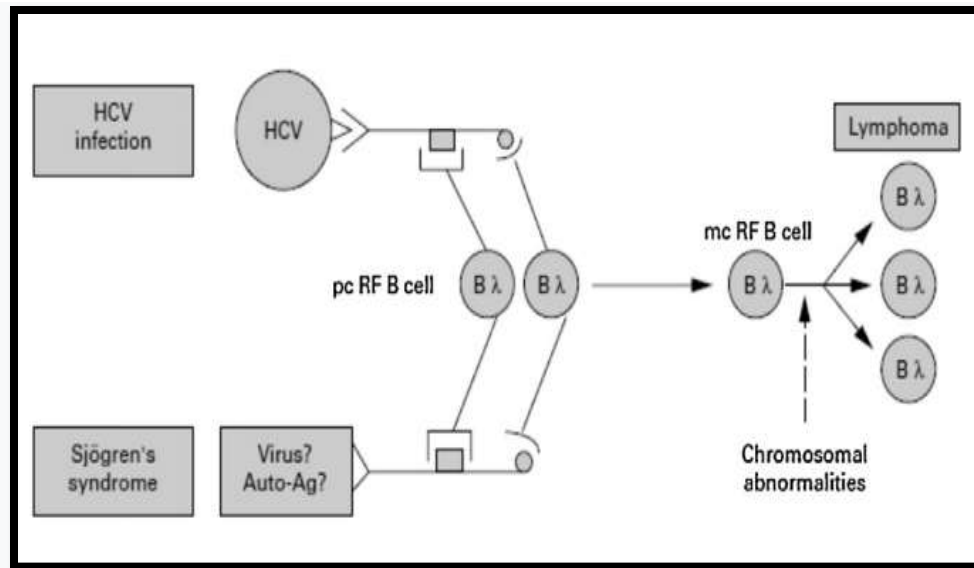


Figure 3:- Common pathophysiology during lymphomagenesis of chronic hepatitis C virus infection and during the primary Sjögren syndrome [14].

Conflict of interest:

None.

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