PRIMARY TESTICULAR LYMPHOMA WITH EXTRANODAL INVOLVEMENT

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Summary.- We report the case of a 65-year-old man who presented with a right testicular mass and synchronous involvement of skin and Waldeyer’s ring. These facts led us to the working diagnosis of malignant primary testicular lymphoma.

METHODS/RESULTS: We present the case with comments and make a bibliographic review of the disease.

CONCLUSIONS: Primary testicular lymphoma is a uncommon testicular tumour that accounts for not more than 9% of all testicular tumours in the series with higher incidence. Testicular lymphomas are also rare among haematopoietic tumours, accounting for just 1% of all lymphomas, but due to their highly malignant histopathology they may become highly aggressive tumours. Patient age at presentation is over 60 years which makes it the most frequent tumour for this age group. 70% of recently diagnosed patients show Ann Arbor stages I and II. Tumours in advanced-stage have a predilection for spreading to extranodal sites such as central nervous system, skin, Waldeyer’s ring and lungs.

Keywords: Testicular neoplasm. Extranodal lymphoma. Testicular lymphoma.

Resumen.- OBJETIVOS: Presentamos un caso de masa testicular derecha en varón de 65 años con afectación sincrónica de piel y anillo de Waldeyer, datos que nos orientan a que se trate de un linfoma testicular maligno por lo característico de la presentación del cuadro clínico.

MÉTODOS/RESULTADOS: Se realiza una presentación y comentarios de las características del caso clínico, así como una revisión de la literatura.

CONCLUSIONES: El linfoma testicular primario es un tumor testicular infrecuente, suponiendo no más del 9% de los tumores testiculares en las series con mayor incidencia; a su vez el linfoma testicular como tumor hematopoyético es infrecuente, con una incidencia del 1% de los linfomas, pero debido a su histopatología en la mayoría de los casos de alta malignidad, les hace ser de los tumores testiculares más agresivos. La edad de aparición es por encima de los 60 años, convirtiéndose en el tumor más frecuente para este grupo de edad. En el momento del diagnóstico el 70% de los pacientes presentan estadios I y II de Ann Arbor. Cuando el debut es en forma de estadio avanzado, las localizaciones extranodales más frecuentes son el sistema nervioso central, la piel, el anillo de Waldeyer y el pulmón.

Palabras clave: Neoplasia testicular. Linfoma extranodal. Linfoma testicular.

INTRODUCTION

First described by Malassez in 1987, primary testicular lymphomas account for approximately 1% of non-Hodgkin’s lymphomas. However, secondary involvement of the testes is more common, and can occur in over 4% of Burkitt-type lymphomas (1). In fact, the name of primary testicular lymphoma is debatable because of the absence of lymphoid tissue in the testicle, and because the majority of patients present systemic
dissemination shortly after diagnosis, in one of these three forms of presentation: (2,3)

- Initial manifestation of an occult lymphoma.
- Testicular involvement of a known lymphoma
- Primary testicular lymphoma, without other organ involvement

Therefore, according to the current literature, primary extratesticular disease must always be considered, and primary testicular lymphoma should only be considered in tumours that do not present with any other tumour masses in the rest of the body, or when such tumours are smaller in volume than the testicular tumour mass.

**CASE REPORT**

65-year-old male with a history of hyperglycaemia on diabetic treatment, and episodes of rectorrhagia with colonoscopy and biopsies negative to malignancy three years ago. The patient was referred to us from A&E, presenting with gradual increase in right hemiscrotum over the past month. For the past fortnight the patient referred to scrotal pain and fever, without associated constitutional symptoms.

Physical examination revealed good general health, good skin and mucous colour. Cardiopulmonary auscultation NAD, normal penis and left testis. Right hemiscrotum increased in size, fixed, reddened skin and painful to palpation.

Transillumination negative. No palpable inguinal adenopathies. Digital rectal examination showed smooth, fibroelastic prostate, volume II/IV. Notable presence of slightly painful, skin nodulation that had suddenly appeared in the past fortnight, located immediately above the upper lip (Figure 1). Mouth-throat examination revealed hypertrophied right tonsil, with an ulcer on the surface (Figure 2).

The only finding of note in the blood test was LDH 603 U/L [230-460]. Testicular tumour markers were within a normal range (α-fetoprotein and βHCG). Normal liver function, total proteins 7.9 g/dl and normal β2microglobulin. PSA 1.4 ng/dl. Blood count showed Hb 14.5 g/dl, Ht 43.4%, leucocytes 7600 x 106/l with normal formula, platelets 298000 and normal coagulation.

Chest X-ray: no relevant findings.

Scrotal ultrasound showed large, solid, highly heterogeneous lesion, with fluid inside, occupying the majority of the testis (Figure 3).

With the diagnosis of right testicular mass due to probable testicular lymphoma, the patient underwent right inguinal orchiectomy. After clamping the spermatic cords, we performed an intra-operative biopsy of one of the 2 stony-solid nodulations in the upper end of the testis. The intra-operative biopsy findings were compatible with lymphoid-like malignant neoplasia with occasional large cells, without distinguishing between lymphoma and seminoma. The definitive macroscopic paraffin study showed a testicle measuring 4.9 x 4.3 x 4 cm and weighing 68 grams. The slice series identified an expansive mass measuring 4.1 cm located in the upper part of the testis, close to the tunica albuginea, but without penetration. Microscopic and immunohistochemical diagnosis confirmed diffuse large B-cell
non-Hodgkin lymphoma with positive immunohistochemical markers for CD20 and Bcl-2, and negative for T markers. The Ki67 cell proliferation index was 70-80% (Figure 4).

The abdominal-pelvic CT extension study performed did not reveal any images to suggest intra-abdominal involvement.

It was classified as IV-A stage, without bone marrow infiltration. The patient was given 6 cycles of R-CHOP (completed in February 2008), suffering the post-chemotherapy neutropenic complication of pneumonia of the left lower lobe, controlled with the corresponding antibiotic therapy.

DISCUSSION

Testicular lymphoma accounts for 1 to 9% of testicular tumours, depending on the studies (3), and it is the commonest malignant testicular tumour in men over the age of 60, accounting for 25 to 50% of testicular tumours in this age group. 23% are bilateral (occurring either at the same time or a different time) and this is a sign of poor outcome.

The aetiology of NHL is largely unknown, although certain factors have been associated with a higher tumour incidence, such as acquired or congenital immunodeficiency conditions, infectious agents, chemical and physical agents.

Congenital diseases such as Ataxia-Telangiectasia, Wiscott-Aldridge, and X-linked lymphoproliferative syndromes have a high incidence in high-grade B NHL.

Similarly, drug or infection-associated immunodeficiency also presents a higher incidence. For example, post-transplant patients have a 25-50% higher risk of developing NHL than the general population. Likewise, it is more common for these tumours to develop in patients undergoing chemotherapy, especially with alkylating agents.

With regard to immunodeficiency from HIV, the risk increases almost 90-100 times in comparison with the general population, and accounts for 25% of testicular tumours diagnosed in younger patients, with more aggressive histology and a poorer prognosis (4).

Diseases such as Sjogren’s syndrome, Hashimoto’s thyroiditis and Coeliac disease promote the development of mucosa-associated lymphoid tissue (MALT) and increase the risk of B-cell NHL.

Infection from Helicobacter Pylori in the stomach promotes the development of chronic gastritis and MALT, with a high association with gastric lymphoma.

Epstein-Barr virus infects and immortalises B lymphocytes. This infection has a high association with Burkitt’s lymphoma and B-cell tumours in immunodeficient patients.

A higher incidence of lymphomas has also been observed in patients exposed to major radiation (atomic bomb or nuclear reactor explosions).

The commonest presentation is spontaneous testicular pain and pain on palpation, accompanied by increased volume and testicular consistency. Presentation of a painless mass is less common. Hydrocele is associated
in up to 40% of patients. A quarter of patients present constitutional symptoms (5).
When the patient presents in an advanced stage, the most characteristic extranodal locations are the central nervous system, skin, Waldeyer’s ring and lungs (6,7).
On analysis, LDH is elevated, in correlation with tumour activity. Other testicular tumour markers are normal.

On ultrasound, hypoechoic masses appear beside areas of normal echogenicity.
The differential diagnosis takes seminoma and granulomatous orchitis into consideration (8). Nowadays, immunohistochemical markers and the classification of lymphoma surface antigens serve to provide a definite diagnosis.

Macroscopically, tumours are greyish-white and their appearance resembles a seminoma. Unlike the seminoma, where there is massive destruction of the seminiferous tubules, the latter are conserved because the tumour process takes place in the peri-canalicicular space. However, spermatogenesis is disturbed in any case.

When prepared, a population of cleaved and non-cleaved large cells is found, with hyperchromatic nuclei and several nucleoles, with elevated mitosis. Diffuse large B-cell lymphoma is predominantly found on histology in 80-90% of cases, and T-cells are exceptional (9).

The first line of treatment is radical orchiectomy in the case of non-advanced stages. In the case of advanced stage tumours, orchiectomy can be postponed until after systemic treatment (1, 5, 10). Bilateral orchiectomy is not indicated for prophylaxis in the case of unilateral tumours (7). The use of local radiotherapy (2500-3500 cGY) is controversial (6,7). Some authors believe it is of little use and others recommend its use in localised stages (I and II), thus preventing the appearance of a contralateral lymphoma (the probability of contralateral relapse is 8-35%), and in turn reducing the dose of chemotherapy in young patients.

The most important prognostic factors are age and tumour stage (Ann Arbor staging, Table I). The histological stock is a secondary prognostic factor because the majority of cases are highly malignant (8). Factors involved in a poor prognosis are advanced age, presence of B symptoms, primary tumour greater than 9 cm, degree of sclerosis, infiltration of the epididymis, cord or vessels.

The extension study consists of a total body CT, bone marrow biopsy and chest X-ray.

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Treatment is based on chemotherapy adjuvant to surgery (or prior to surgery in advanced stages), because in localised stages, surgery alone carries a 90% risk of relapse within two years.

Standard chemotherapy for NHL is 6 cycles of CHOP regime (cyclophosphamide, adriamycin, vincristine and prednisone), adding etoposide or rituximab which markedly improves the antitumour response and the prognosis in turn. Rituximab is a monoclonal antibody that targets CD-20 surface antigens, which are present in almost all B-cell lymphomas. In our patient, we also gave Rituximab together with CHOP.

In advanced stages, survival is not usually more than 2 years, justifying the use of intrathecal chemoprophylaxis of the central nervous system (5, 10).

In any case, primary testicular lymphomas tend to have an aggressive evolution with 5-year survival standing at 10 to 40%, depending on the study. They tend to spread rapidly, with a highly characteristic involvement in advanced stages of extranodal locations such as Waldeyer’s ring, central nervous system, skin, lung and bone marrow, negatively affecting the prognosis (5, 7, 10).

CONCLUSIONS

B-cell non-Hodgkin testicular lymphoma is an uncommon, but not a rare disease. Extranodal locations suggest a poor prognosis, and relapse occurs in localised stages within two years in over 90% of cases. Diagnosis is often late and is delayed in the majority of cases through confusion with chronic bacterial orchitis.

In our case, the diagnosis was not delayed because the patient presented with pain. With regard to diagnosis and treatment consisting of unilateral orchietomy and subsequent systemic CHOP-type chemotherapy, we followed the directives guided by experience in these cases and although follow-up is still short, our patient is alive and has not had any tumour relapse.

Despite this being a highly malignant tumour process, a therapeutic approach combining surgery, chemotherapy, radiotherapy and monoclonal antibodies such as rituximab, leads to a cure in 50% of cases. This is achieved by means of an interdisciplinary effort of urologists, oncologists, radiotherapists and medical physicians.

REFERENCES AND RECOMMENDED READINGS

(*of special interest, **of outstanding interest)