Nasal-type NK non-Hodgkin lymphoma in the testis

Busto-Martín Luis, Pombo-Otero Jorge, Busto-Castañón Luis

ABSTRACT

Objective: To present a case of nasal-type NK-cell tumor arising in the testis along with a review of the published biomedical literature.

Methods and result: Patient is a sixty-eight-year-old man with no prior urological history who sought medical attention at the authors’ department for inflammation of the right testis of 11-month progression affecting scrotal skin that responded poorly to antibiotic treatment. Inguinal orchiectomy was carried out and affected skin was resected. Definitive histological diagnosis was large cell nasal-type, NK cell non-Hodgkin lymphoma. The Hematology Department later carried out extension study that confirmed lymphoma diagnosis through blood smear. Patient was staged and then received three cycles of cyclophosphamide, doxorubicin, oncovin, and prednisone chemotherapy and intrathecal prophylaxis. At follow-up twenty months from the time of symptom onset patient has not presented with disease involvement in lymph nodes or in any other organ.

Conclusions: Nasal T/NK-cell lymphomas are rare tumors in the Mexican population and extranasal presentation is extremely rare with only twelve cases of testicular presentation reported in the literature reviewed. Anatomicopathological study by means of immunohistochemistry is essential for classifying these lymphomas given that this type is characterized by rapid dissemination and poor treatment response.

RESUMEN

Objetivos: Comunicar un caso de un tumor de células NK de tipo nasal originado en el testículo y realizar una revisión de la literatura biomédica publicada.

Métodos y resultado: Presentamos un paciente de 68 años de edad, sin historia urológica previa, que acudió a nuestra consulta refiriendo desde hace 11 meses clínica de inflamación del testículo derecho y afectación de la piel escrotal, con mala respuesta a tratamiento antibiótico. Se realizó una orquiectomía por vía inguinal y se resecó la piel afectada. El diagnóstico histológico definitivo fue de linfoma no Hodgkin tipo NK nasal de células grandes. Posteriormente, fue derivado al servicio de Hematología que realizó un estudio de extensión confirmando con un frotis sanguíneo el diagnóstico de linfoma y tras estadiificar al paciente se realizó un tratamiento sistémico con tres ciclos de CHOP y profilaxis intratecal. Tras 20 meses de seguimiento desde el inicio de los síntomas el paciente no ha presentado afectación ganglionar o de algún otro órgano.

Conclusiones: Los linfomas de células T/NK nasales, son tumores poco frecuentes en nuestro medio, siendo su presentación extranasal toda una rareza y encontrado en la literatura revisada sólo 12 casos de esta presentación testicular. Es esencial el estudio anatomicapatológico mediante inmunohistoquímica para clasificar dichos linfomas, ya que este tipo se caracteriza por una rápida diseminación sistémica y mala respuesta al tratamiento.
INTRODUCTION

Nasal natural killer (NK) lymphomas represent a small portion of all non-Hodgkin tumors. Their extranodal presentation, known as nasal-type NK lymphoma, is the most frequent, even though it is rare. These tumors are characterized by extensive vascular destruction and prominent tissue necrosis and the habitual extranodal site is the upper respiratory tract, especially the nasal cavity.

The following case is presented as a rare entity, since its confusion with other more common pathologies such as chronic orchiepididymitis that responds poorly to antibiotics can produce diagnostic and treatment delay.

This type of nasal-type NK lymphoma is characterized by poor prognosis and short-term systemic dissemination with poor response to current treatments.

CASE PRESENTATION

Patient is a 68-year-old man who sought medical attention at the authors’ service for pain and inflammation of the right testis of 11-month progression that was responding poorly to antibiotic treatment. Past medical history includes angiotensin converting enzyme (ACE) inhibitor intolerance, chronic obstructive pulmonary disease (COPD), deep vein thrombosis (DVT), chronic anemia, and various hospitalizations for respiratory infection and secondary heart failure.

Two-months earlier, patient complained of inflammation in right testis accompanied with continuous pain and occasional dysuria but did not present with fever or any other symptom of interest. Prior to being seen at the authors’ service, the patient’s primary attending physician had ordered 2 urine cultures (one was positive for multisensitive E. coli and the other was negative), two 10-day regimens of wide-spectrum antibiotics (750 mg oral ciprofloxacin every 12 hours and 875/125 mg augmentin every 8 hours). Despite partial improvement, patient had symptom recurrence after finishing treatment.

Physical examination showed patient to be without fever, in good general state of health, with slightly pale skin and mucosa. Right scrotum was slightly hardened. Left testis was normal and right testis had an irregular aspect upon palpation, was slightly painful, and epididymis was thickened. No inguinal adenopathy or other type of alteration was observed.

Full blood count showed chronic anemia (Hb= 9.9, HCT=32 with microcytosis and anisocytosis). Leukocytes and lymphocytes were in the normal range. Urinalysis reported urinary pH of 5, negative nitrites, esterase +, and leukocyturia of 15 leukocytes/field.

Possible chronic epididymitis secondary to microbacteria was contemplated due to test results and poor response to antibiotics, and so scrotal ultrasound, Ziehl-Neelsen stain, and acid-alcohol-resistant bacillus (BAAR) culture in urine were ordered. Scrotal ultrasound revealed thickening of right scrotal skin, testicular parenchyma compression of the tail and body of the right epididymis, and small gross calcifications. These findings were described as possible chronic epididymitis without being able to rule out tuberculous pathology (Images 1 and 2).

In the interim before microbiological results were available, chest and abdominal films and renovesicoprostate ultrasound were ordered that revealed no pathology of interest. Bacteriological results were negative and so patient was put on the waiting list for orchiectomy because he continued to have chronic epididymitis with poor antibiotic response that was beginning to affect the scrotal skin.

Once admitted to the hospital, patient underwent inguinal orchiectomy with resection of partial region of the scrotum since there was subcutaneous cellular tissue necrosis. During postoperative period surgical wound progressed poorly developing seroma that required treatment with ionized silver (Aquacel®) solution.

Surgical specimen weighed 110 g, testicular parenchyma was substituted by a dense, yellowish, necrotic-looking tissue that affected the albuginea, subcutaneous tissue, and skin, causing cutaneous ulcers. Microscopic description showed infiltration of the testis, albuginea layer, muscle layer, and skin by lymphoid-type cells with important pleomorphism and distribution in very angiocentric areas. The cells had...
large, irregular nuclei with prominent nucleoli and frequent mitosis that surrounded vascular structures and produced wide areas of necrosis. Immunohistochemical study with monoclonal antibodies showed CD3+, weak focal positivity with CD56, MIB-1+, and Epstein Baar virus positivity according to the Eber technique. Cells were negative for CD5, CD20, CD 30, CD 75, BCL-2, and BCL-6. These neoplastic cells had NK cell phenotype providing definitive diagnosis of nasal-type non-Hodgkin NK lymphoma of testicular localization with infiltration into the scrotal skin.

After this diagnosis, patient was sent to the Hematology Service where chest-abdominal-pelvic computed tomography (CT) scan was ordered as extension study along with a blood smear. Blood smear showed cytologic profile corresponding to lymphoma while the CT scan did not identify any suspicious adenopathy or visceromegaly. Patient was given 3 systemic chemotherapy cycles with the cyclophosphamide-hydroxydoxorubicin-vincristine-predisone (CHOP) regimen with intrathecal prophylaxis. He required emergency room treatment for fever, nausea, vomiting, and diarrhea due to septic shock brought on by postchemotherapy aplasia that was resolved with wide-spectrum antibiotics and transfusion support.

Patient has since been under out-patient control and up to the present date 4 cerebrospinal fluid cytology studies have been negative. At twelve months since testicular symptom onset and 6 months after definitive diagnosis, patient is alive and complete body CT scan has shown no evidence of visceromegaly or lymph node involvement (Image 3).

**DISCUSSION**

Primary lymphoma of the testis makes up 1% of all non-Hodgkin lymphomas (NHL). The entity designated by the World Health Organization was previously known as angiocentric lymphoma or lethal midline granuloma. These types of lymphomas are usually diagnosed in adults and mean age is 50 years with a 3:1 predominance of men to women. Incidence of these lymphomas is much higher in Asian and South American populations and the majority of studies on this pathology are from those countries. It is possible that there are lifestyle and environmental factors that contribute to the greater incidence seen in these populations.

Primary origin of 80% of these types of lymphomas is in the nasal cavity (and are called nasal T/NK lymphoma) and manifest as ulcerated nasal mass usually accompanied with purulent and bleeding rhinorrhea. In 20% of patients the tumor primarily affects sites outside the nasal cavity (known as nasal-type T/NK lymphoma), including the upper respiratory system, skin, gastrointestinal tract, spleen, lung, brain, soft tissues, and testes. The present authors found only 12 testicular cases published in the literature reviewed. In these cases it is important to explore the nasal cavity to confirm that the disease is really nasal-type lymphoma and not primary nasal lymphoma with systemic metastases. Patients most commonly present with systemic involvement but without lymphadenopathy, which can hinder diagnosis.

Clinical course usually progresses rapidly, involving various extranodal regions and disease is often in advanced stage at the time of diagnosis. In the majority of cases malignant cells are not found in blood smears or bone marrow aspiration studies.
There is no satisfactory classification for this type of lymphoma, although stratification is usually done with the Ann Arbor classification system. International Prognostic Index (IPI) which indicates age, stage, lactate dehydrogenase (LDH) level, extranodal sites, and general state of health is also useful for evaluating disease seriousness.10

Inguinal orchiectomy and resection of the affected tissues is essential given that anatomicopathological cell study is conclusive for diagnosis.

Histologically it is common to find angiocentric pattern and cell expression with T/NK phenotype. Definitive diagnosis is made through immunohistochemistry with NK cell marker expression (positive for CD56 glycoprotein and CD3- on the surface, although CD3+ cases have been described). It has been suggested in some publications that CD56 expression can explain extranodal localization of these lymphomas since a homophilic adhesion molecule is expressed in the lymphoid system, in the brain, nerves, and epithelial cells of the rete testis. 9

Rearrangement of T-cell receptor (TCR) genes is not common, however, similar cases have been described in which TCR is not found in the germline. Those cases could be considered to be nasal-type T/NK lymphomas or alternatively, T lymphomas with unusual phenotype (CD56 and Epstein-Baar virus (EBV) positive) 11. By means of in situ viral RNA hybridation, an important association with EBV has been found (up to 90% of presentations whether their localization is nasal or extranasal).

In the testicular type, due to the fact that this type of pathology is not often expected, once orchiectomy is performed and diagnosis confirmed, extension study with CT scan or nuclear magnetic resonance (NMR) imaging should be carried out.

While patients with disease of nasal origin are usually treated initially with radiotherapy, those with extranasally localized tumor, such as the present case, can also benefit from complementary local radiotherapy; even so it is known that these types of tumors present with rapid systemic dissemination and therefore it is common to associate systemic chemotherapy from the beginning.6 There are many studies with experimental protocols that include L-asparaginase, especially from Asian countries where greater disease incidence exists, and they have reported significant survival improvement.

Chemotherapy results are far from satisfactory, and multiple regimens have been carried out with no favorable results. The majority of patients die within the first year of diagnosis. Due to the scarcity of existing cases, all published reports are based on retrospective patient series and optimum treatment has yet to be established. Nasal T/NK lymphoma has been studied more, resulting in very little information available on disease with extranasal localization. The most frequent regimens found in published reports are 3 cycles of CHOP, accompanied in some cases with intrathecal methotrexate (MTX) prophylaxis.10 Currently combinations of radiotherapy and chemotherapy are being used in disease with nasal localization, while in extranasal disease (as in the present case) mass exeresis is first carried out (diagnostic biopsy is sufficient) and treatment is completed with chemoradiotherapy if disease is localized and chemotherapy if there is systemic involvement.12 Prophylactic radiotherapy is carried out on certain occasions on the contralateral testis, the pelvic lymph node chain, and even the brain due to the important number of existing central nervous system (CNS) presentations.6,10,13,14

Despite the effort to test different therapeutic managements, the present authors found no published study in which complete disease remission has been achieved.

Due to these different treatment line failures, the considerable aggressiveness of these types of tumors, and the short survival rate with current therapies, some physicians have considered bone marrow or pluripotential peripheral cell transplantation as alternative treatment in cases in which patient vital status and disease stage are adequate.

■ CONCLUSIONS

A case of primary nasal-type T/NK cell lymphoma of the testis is presented. This type of tumor is extremely rare,
even in the Asian countries where these lymphomas are more frequent and only 12 published cases of primary T/NK cell lymphoma of the testis have been found by the present authors. In contrast to the T/NK lymphoma that affects the nasal cavity and nasopharynx, tumors such as the one described here progress rapidly and end the life of the patient in a short period of time. Definitive diagnosis is made through immunohistochemical study of the surgical specimen. Treatment should be multidisciplinary (with chemotherapy and/or radiotherapy). Nevertheless, there is no current protocol that significantly prolongs survival in these patients.

BIBLIOGRAPHY