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Research Article

Sertoli Cell Tumor of the Testis in Association with Peutz-Jeghers Syndrome Sometimes Requires a High Index of Suspicion

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Abstract

Peutz Jeghers Syndrome (PJS) is an autosomal dominant disorder characterized by mucocutaneous pigmentation and hamartomatous polyps throughout the gastrointestinal tract. Pigmented macules appear especially on oral mucosa, lips and fingers. Hamartomatous polyps are found predominantly at the small intestine and colon lesser extent¹ and can cause bleeding and abdominal pain secondary to intussusception, intestinal obstruction and infarction. Approximately 80% of patients with PJS have mutations in threonine kinase 11 (STK11) located in 19p13.3 chromosome^{1,2}. This acts as a tumor suppressor gen, leading its mutation to increased risk of cancer at an early age³. Most commonly reported cancers are luminal gastrointestinal and breast. Testicular tumors are less known, but may be present

at early age² and course with estrogenic manifestations in most of cases.

We report a case of PJS with intratubular large cell hyalinizing Sertoli Cell (LCHSC) tumor of the testis diagnosed during the follow-up of the patient.

Keywords: Peutz-Jeghers syndrome, testicular neoplasm, Sertoli cell tumor, gynecomastia.

Introduction

Peutz Jeghers syndrome (PJS) is an AD disorder with variable penetrance and expressivity that is typically characterized by mucocutaneous pigmentation and gastrointestinal hamartomatous polyps. Pigmented lesions clinically manifest as perioral melanosis on the oral mucosa, fingers and tongue. Typically absent at birth, they developed during childhood and decrease throughout the years. The hamartomatous polyps are located predominantly at the level of the small intestine and can cause chronic abdominal pain, bleeding and intussusception, but their malignant degeneration is rare. Many patients with PJS have a mutation in the STK11 gene (with an estimated incidence of 70% cases), tumor suppressor gene located on the short arm of chromosome 19, which predisposes them to suffer various types

of malignancies. Testicular injuries can suffer these patients are less well known and may debut as early as childhood. In most of the cases described, they are associated with estrogenic manifestations, where gynecomastia secondary to increased activity of the aromatase enzyme is characteristic.

To our knowledge, there are only two series of patients published for this purpose: 4 cases filed in 2001 and the last dating from 2008 where 8 cases of large cell testicular tumor associated with sertoli SPJ. The rest of the publications present isolated cases of patients suffering from this syndrome still a total of 24 cases reported worldwide.

Case Report

A child with family history of PJS in mother and grandmother was referred to our hospital with four years old because of prolapsed rectal polyp. Polypectomy was carried out and genetic study confirms the PJS, with a deletion that includes exons 2 to 10 of STK11 gene.

During his childhood polypectomy was necessary at eleven years old for polyp removal in mid-jejunum, hepatic flexure colon and sigma due to abdominal pain and chronic lower gastrointestinal bleeding. A year later three polyps in the rectum were excised. All removed polyps were hamartomatous, without atypia or malignancy signs.

At the age of 12 years and four months, testicular ultrasonography was performed as part of the monitoring protocol. Testicles were slightly increased in size and there were multiple echogenic images (Fig. 1) predominantly in right testis due to calcification, the larger 2.6mm. (Fig.2) The patient was asymptomatic.

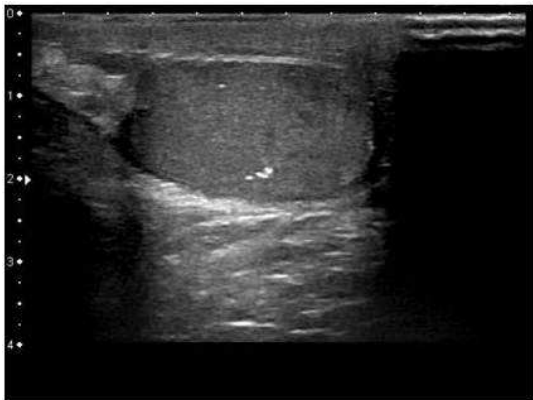


Fig. 1: Testicular Ultrasound Showing Multiple Calcifications



Fig. 2: Testicular Echogenic Images, the Larger 2.6mm, in the Right Testis.

On physical examination the boy had perioral melanosis, pubertal stage G2P2 and testicular volume of 6 ml. In the context of obesity, he presented adipose tissue in breast, with little glandular tissue support mild gynecomastia. Laboratory tests showed LH: 2.1 mIU/ml (normal range: 1-12), FSH: 1 mUI/ml (normal range 1-12), total testosterone: 69 ng/dl (normal value for Tanner 2) and estradiol <10pg/ml. Growth velocity was normal and bone age according to chronological age.

Because of ultrasound findings testicular biopsy was performed. It revealed testicular maturation slightly delayed for age with no spermatogonial proliferation. On this maturational delay, isolated tubules were observed with varying thickening of the basement membrane. Inside tubules stands Sertoli cells, with wide eosinophilic cytoplasm and a nucleus with spherical small

nucleoli. No atypia or mitosis were found (Fig. 3 and 4). All of these histological findings are consistent with LCHSC.

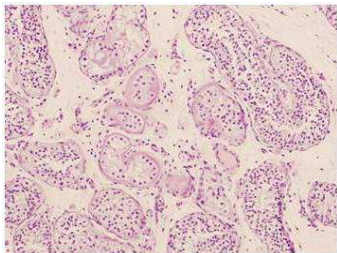


Fig. 3: Seminiferous Tubules with Thickened Basement Membrane without Germ Cells and Sertoli Cell Proliferation with Slightly Enlarged Nuclei and Large Cytoplasm.

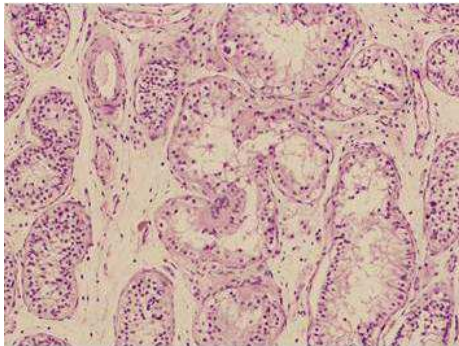


Fig.4: The Nests are the Foci of Intratubular Neoplasia Sertoli Cells. Around the Tubules are Some Germ Cells but Not Observed Mature Germ Cells.

Comment:

Patients with PJS may develop testicular neoplasms in a variable percentage of cases⁴. These belong to stromal tumors derived from Sertoli cells⁵. The large-cell calcifying Sertoli cell tumor was first described by Proppe and Scully⁶. In most cases it appears in phenotypically normal patients as a single, firm nodule but up to one third of cases⁵ are associated with genetic or endocrine syndromes as Carney Syndrome or PJS. In such cases neoplasms are commonly bilateral, multifocal, smaller and they appear earlier^{5,7}, as in our patient. The testicular lesion specifically associated with PJS is called Intratubular large cell hyalinizing Sertoli Cell (LCHSC) neoplasia⁷ and is similar to the sex cord tumor with annular tubules of the ovary that appears in women with PJS⁸.

Histologically, the lesion shows a patchy distribution of enlarged tubules, which exceed several times the diameter of unaffected tubules. Sertoli tumor cells are large with vacuolated and eosinophilic cytoplasm. Tubules can be replaced by basement membrane deposits, giving a hyalinized appearance⁷. Another feature is the presence of calcifications, not always present in cases of PJS^{7,9}, but seen in our patient. In some cases Intratubular Sertoli Cell Proliferations (ISCPs) have been described. They emerge from seminiferous tubules and gradually replace the cell population. There is controversy about whether ISCPs are non-neoplastic proliferative lesions with malignant potential or represent an intraepithelial stage of tumor development. Although in some patients ISCPs are the only pathological finding, they may appear nearby to large-cell calcifying Sertoli cell

tumor¹⁰. Some authors argue that they are the testicular neoplasm specifically associated to PJS^{7,11}.

Extratubular growth implies potentially malignant nature irrespective of local characteristics⁴. Malignancy is found in approximately 17% of patients with large-cell calcifying Sertoli cell tumor⁹, usually in older patients with unilateral and unifocal mass^{8,9}. In patients with PJS reviewing of published cases finds that local infiltration is very uncommon, so the process often remains confined to the tubules for long periods of time². Anyway, it should be note that the follow-up period of these patients is limited since first cases date from the 80's and progression to invasive tumor cannot be rule out¹². Venara et al¹⁰ described a patient with a follow up of more than 30 years with no evidence of progression. Although histological malignancy

index have been described (high mitotic rate, nuclear atypia, necrosis and vascular or lymphatic invasion)^{8,9}, the question of which damage may progress is still unknown⁷.

Tumor cells have increase activity of aromatase enzyme¹⁰, which normally is produced by Leydig cells⁹. This determine a higher conversion of testosterone to estradiol. As a result, patients with LCHSC typically have clinical signs of estrogenic activity that lead to the suspicion of the tumor, such as acceleration of growth with advanced bone age⁹ and gynecomastia¹⁰. However, cases of incomplete penetrance have been already described¹⁵ and peripubertal gynecomastia not necessarily related to the tumor was appreciated in our patient.

The course of evolution of this condition justifies its conservative management monitoring by ultrasounds. Surgery could be indicated in selected cases of unusual invasive tumors, pain or mass effect. Hormonal manifestations could be treated with aromatase inhibitors¹³, like testolactone and anastrozol. These drugs can be effective in controlling the clinical features of the disease, like breast development, growth velocity and bone maturation¹⁶ but evidence is limited and further studies are required⁹. In our patient no hormonal abnormalities were found and bone age and growth was normal so it was decided to keep monitoring. Later ultrasound controls show no change compared to previous.

The case reported here represents an unusual presentation because it appears in an asymptomatic boy with almost no

estrogenic manifestations unless mild gynecomastia. The lesion was diagnosed during a routine check, which should make us question the kind of monitoring strategies in these patients with increased risk of cancer. In case of testicular neoplasms surveillance strategies are based on expert opinion only. It is recommended to perform annual physical examination and ultrasound in case of detection abnormalities or signs of precocious puberty¹. Anyway, it should be noted that average age of presentation of these tumors is earlier than in others cancers associated to PJS^{1,4,8}. As in our case, diffuse and bilateral testicular involvement can overlook the presence of changes on physical examination¹³ and the development of secondary hormonal disturbances may not be present at an early stage. Hyperestrogenism cannot be detected in laboratory tests because

the hormone excess is limited to testicular aromatase¹⁴, which may explain the findings in our patient.

Conclusions

Our case highlights the need to establish a high index of suspicion of testicular tumors in patients with PJS. Although LCHSC usually remains confined locally, can lead to endocrine disorders with impact on growth and pubertal development in children. It is necessary to establish preventive diagnostic strategies from an early age in these patients.

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