

In our patient a blood-borne infectious site with no apparent origin was found after an extension study.

Virtually any bacterium may infect the thyroid gland,⁸ including pneumococci, *Salmonella*, *Klebsiella*, *Bacteroides*, *Treponema pallidum*, *Pasteurella* spp., and mycobacteria. Some organisms may cause chronic or insidious infection, particularly in patients with HIV disease. These include *Mycobacterium tuberculosis*, atypical mycobacteria, *Aspergillus* spp., *Coccidioides immitis*, *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Candida* spp., *Treponema pallidum*, *Echinococcus* spp., and *Pneumocystis carinii*.

The dominant clinical symptom is pain in the thyroid gland region, with a subsequent increase in thyroid size and temperature. Our patient also reported dysphagia, but had no other symptoms such as hoarseness, sore throat, or dysphonia.⁹ Local lymphadenopathies were not found either. When faced with this presentation, a neoplastic condition must be ruled out. As occurred in our patient, thyroid infection most commonly occurs in autumn and winter, usually after upper respiratory tract infections.

Thyroid function tests showed no changes, as usually occurs in cases of pyogenic thyroiditis.

Thyroid gland ultrasound for fine needle aspiration is the initial imaging test of choice for diagnosis.

A CT scan may be of value for abscess site identification, but this is only required in exceptional cases.

Empirical treatment should be started with broad spectrum parenteral antibiotic therapy based on suspected diagnosis after radiodiagnosis.¹⁰ Surgical exploration should be performed in all patients in whom anatomical changes such as piriform sinus fistula or a thyroglossal duct remnant are found. Surgical drainage should be performed whenever imaging tests show the presence of intraglandular abscess or gas formation. If necrosis occurs or infection persists despite adequate antibiotic therapy, thyroid lobectomy will be required.³

Although 14 days of antibiotic therapy are sufficient to treat pyogenic thyroiditis, treatment prolongation up to four weeks is advised when bacteremia is found.

In conclusion, pyogenic thyroiditis is a very uncommon condition usually occurring in patients with thyroid diseases,

piriform sinus fistula and, especially, with immunosuppression. Our patient did not meet any of these characteristics, which makes the case even more unusual.

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Neurohypophyseal germinoma: hCG in cerebrospinal fluid as a key for a diagnostic challenge

Germinomas neurohipofisarios: hCG en líquido cefalorraquídeo como pieza clave para un reto diagnóstico

Neurohypophyseal germinomas are rare neoplasms, with slow growth and variable clinical presentation that occasionally complicate their diagnosis in the early stages of the disease. Although the determination of human chorionic

gonadotropin (hCG) in serum and cerebrospinal fluid (CSF) may help, definitive diagnosis of these tumors is determined by the histopathological findings. We present two new cases of germinomas with special features that delayed their diagnosis for several years, and a review of the literature on this pathology.

A 14-year-old boy was referred to our department because he presented growth arrest for the previous two years. Seven years before he had been evaluated for an incipient mammary button, and four years ago he had been diagnosed of primary polydipsia. Physical examination emphasized height and weight below the 3rd percentile, button left breast and testicular volume of 6 mL. The endocrine study that we performed,

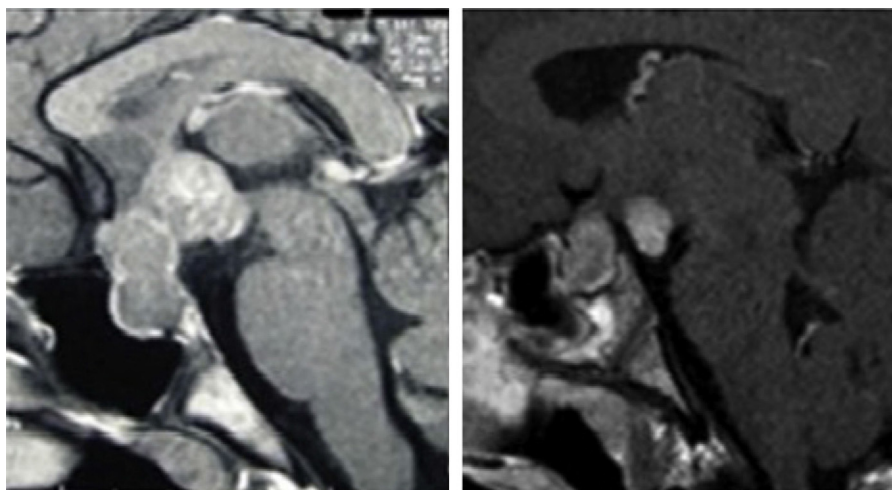


Figure 1 Hypophyseal MRI findings, Sagittal acquisitions, T1-sequencing after gadolinium contrast injection. Case 1. Hypothalamic-hypophyseal lesion affecting both cavernous sinuses, compression of the optic chiasm and deformation of the third ventricle. Case 2. Thickening of the hypophyseal stalk and enhanced uptake nodule in the *tuber cinereum*, measuring 7 mm in size.

revealed anterior panhypopituitarism with hyperprolactinemia: T4L 6.4 pmol/L [normal values (nv), 10.3–25.7] TSH 2.44 mU/L (nv, 0.38–4.84), baseline cortisol 190 nmol/L (nv, 221–690), LH <0.1 U/L (nv, 2–13.8), FSH 0.1 U/L (nv, 2–13.8), testosterone 8.1 nmol/L (nv, 10–35), PRL 28.4 µg/L (nv, 4.6–21), GH 1.6 µg/L (nv, 0–5), IGF-1 143 µg/L (nv, 112–450), and a GH peak after clonidine stimulation test of 1.3 µg/L (60 min). Given the presence of inappropriate undetectable LH concentrations for the testosterone levels, serum hCG was evaluated, yielding a concentration of 10.9 mIU/mL. Brain MRI identified a hypothalamic-hypophyseal mass (Fig. 1). The CSF showed an hCG concentration of 32.6 mIU/mL, with a CSF/serum hCG ratio of 2.9. A transsphenoidal biopsy of the lesion was obtained, with confirmation of the diagnosis of neurohypophyseal germinoma.

A 10-year-old boy presented with polyuria–polydipsia regarded as corresponding to primary polydipsia. Arrested growth was established after one year of follow-up, and the

patient was referred to other hospital where somatotrophic deficiency was detected (GH peak after clonidine stimulation test of 3.6 µg/L at 60 min), along with central diabetes insipidus (dehydration test suspended after 4 h due to hypernatremia (155 mmol/L) and 3% body weight loss). The brain MRI findings proved normal. Treatment was started with GH and inhalatory desmopressin. After 16 months the patient developed central hypothyroidism and replacement therapy was started. A new pituitary MRI revealed then a thickening of the hypophyseal stalk associated to a 7-mm nodule with enhanced contrast uptake in the hypothalamic *tuber cinereum* (Fig. 1). GH treatment was suspended. Transsphenoidal biopsy of the sellar component reported lymphocytic hypophysitis. GH treatment was resumed, with the introduction of corticoid therapy for four weeks and a new pituitary MRI was performed showing a progressive enlargement of the hypothalamic lesion and thickening of the hypophyseal stalk. GH treatment and corticoid therapy were suspended and serum hCG was measured proving low but detectable

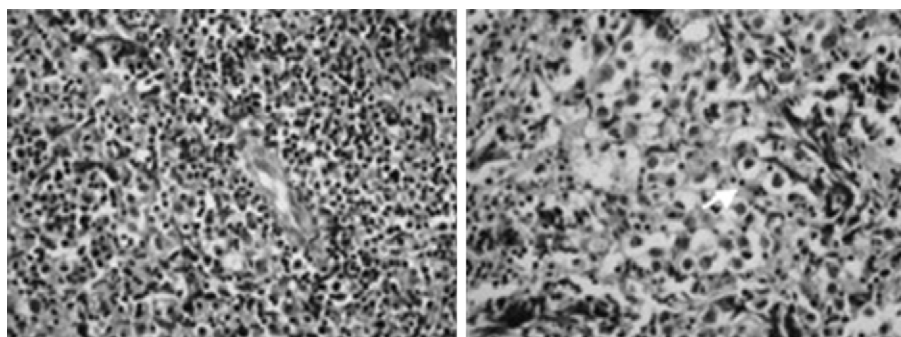


Figure 2 Histological specimen of transsphenoidal biopsy of case 2. Adenohypophyseal tissue showed a dense mononuclear inflammatory infiltrate (left image) with the occasional presence of small granulomas composed of epithelioid histiocytes compatible with lymphocytic hypophysitis. Of note was the presence of large cells with a vesicular nucleus, a macronucleolus and clear cytoplasm, forming small nests delimited by lymphocytes (right image).

levels: 2 mIU/mL. So a second biopsy was performed which again confirmed the diagnosis of lymphocytic hypophysitis (Fig. 2). At this point the patient was referred to our department. We measured hCG levels in serum and CSF with the following results: 7.1 and 23 mIU/mL, respectively, so we asked our pathologist to review the pituitary biopsy performed in the referral center. The adenohypophyseal tissue showed a dense mononuclear inflammatory infiltrate with the occasional presence of small granulomas composed of epithelioid histiocytes compatible with lymphocytic hypophysitis. However, of note was the presence of large cells with a vesicular nucleus, a macronucleolus and clear cytoplasm, forming small nests delimited by lymphocytes (Fig. 2). The immunohistochemical study proved positive for c-Kit and placental lactogen, and negative for CD30, thus confirming the biochemical diagnosis of germinoma.

Intracranial germ cell tumors represent less than 1% of all intracranial neoplasms, but in children constitute up to 6.5% of such lesions.¹ These tumors include germinoma, embryonal cell carcinomas, and teratomas. After the pineal gland, the suprasellar region represents the second most common site of involvement. They are more common in the second decade of life, with a peak incidence between 10 and 14 years of age. The lesions originating in the pineal gland are more prevalent in males, while no gender difference in distribution is seen in the lesions appearing in the suprasellar region.²

Among the suprasellar germ cell tumors, the most common lesions are germinomas, followed by teratomas and pinealomas of an ectopic or metastatic nature.² Neurohypophyseal germinomas may be pure or contain syncytiotrophoblastic giant cells which secrete hCG. Measurement of hCG is an important adjunct method in the diagnosis of germ cell tumors. At high concentrations hCG can be detected in serum, but when the serum hCG levels are low, evaluation of the hormone in CSF may be of help in establishing the diagnosis, since this parameter is more sensitive as an indicator of tumor presence and even can precede to abnormalities on imaging techniques.³⁻⁵

The suprasellar germinomas often generate endocrine alterations. Over 90% of patients show clinical evidence of hypopituitarism that can manifest as gonadal dysfunction, secondary hypothyroidism and less frequently, alterations of the corticotrophic axis. Children may present lack of sexual development and growth alterations as in our two patients. Neurohypophyseal and stalk dysfunction can manifest as hyperprolactinemia (symptomatic or otherwise), or as diabetes insipidus. The latter is observed in about 80% of all cases and may constitute an early finding. As an antecedent, our two cases were initially diagnosed with "primary polydipsia". Other potential symptoms are vision disturbances, including field defects or optic atrophy, hypothalamic manifestations, hydrocephalus, or symptoms of intracranial hypertension.³

In the MRI studies, thickening of the hypophyseal stalk is the most common finding, together with the loss of neurohypophyseal hyperintensity in T1-weighted sequences, in which the lesion appears isointense or slightly hypointense with respect to the normal hypophysis. After gadolinium contrast injection, uptake is less pronounced than in the normal hypophysis.⁵

The imaging findings are not specific and the differential diagnosis fundamentally must be established with tuberoinfundibular lymphocytic hypophysitis.⁶ Since this disorder is infrequent in childhood, histological findings compatible with a lymphocytic inflammatory process can represent the first sign of a host reaction to occult germinoma, as illustrated in our second patient. This would justify the determination of hCG in CSF in all prepubertal patients with a presumed or histological diagnosis of lymphocytic hypophysitis, as well as the immunohistochemical study of the histological specimen with the determination of placental lactogen, c-Kit and CD30.⁷

As regards the treatment of intracranial germinomas, combined chemotherapy-radiotherapy has been the standard approach. However in non disseminated intracranial germinomas, the irradiation of the whole ventricular system without chemotherapy could be sufficient, as recent articles have shown that focal radiotherapy plus chemotherapy were associated with inferior control of these tumors, and a higher incidence of chemotherapy related toxicities.⁸⁻¹⁰

The prognosis of these tumors is dependent upon the histology, but also upon the size of the tumor and the extent of the disease at the time of diagnosis. An early diagnosis is key to treat such tumors before the hypothalamic-hypophyseal damage proves irreversible or adjacent structures suffer compression or metastatic disease became apparent.

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Complete androgen insensitivity syndrome with persistent müllerian remnants. A case report[☆]

Síndrome de insensibilidad completa a andrógenos con persistencia de restos mullerianos. Descripción de un caso

Sex differentiation is a process that starts early during embryogenesis. In males, the SRY gene, located in the short arm of chromosome Y, encodes for the testis-determining factor, which causes the gonad to differentiate into testis. Testicular androgen synthesis by Leydig cells starts from the eighth week of development. It is initially stimulated by placental chorionic gonadotropin (HCG), and subsequently by luteinizing hormone (LH). Fetal gonadotropins stimulate the testicular production of antimüllerian hormone (AMH), which stimulates the regression of müllerian ducts in males. Testosterone, whose action starts in the ninth week once the androgen receptor (AR) is present, allows for the stabilization of wolffian ducts and their differentiation into epididymis, deferent duct, and seminal vesicles. The conversion of testosterone into its most active metabolite, dehydrotestosterone (DHT), allows for the growth of the genital tubercle to form the penis and ventral raphe closure, so forming the penile urethra and scrotal raphe (Fig. 1).

Complete androgen insensitivity syndrome (CAIS) is an XY sexual development disorder where AR function loss exists. CAIS occurs in subjects with the 46 XY karyotype with external genitalia of the female phenotype.

We report the case of a term newborn delivered after a physiological pregnancy. She was the first daughter of healthy, non-consanguineous parents. Birth weight was 3420 g and birth length 50 cm, while the Apgar score was 9–10. Physical examination disclosed normal external female genitalia and two 1-mm masses in both inguinal canals, which led to inguinal hernia being suspected. Abdominal ultrasound examination revealed a persistent peritoneo-vaginal process in both inguinal regions with herniation of abdominal contents and two homogeneous ovoid formations 1 cm in diameter with Doppler flow inside, with no follicles suggesting gonads. At two days of life, LH and follicle-stimulating hormone (FSH) levels were less than 0.1 IU/L (reference values (RV): 0.02–7.0 mIU/L), testosterone was 1.45 nmol/L (RV: 0.42–0.72 nmol/L), and the

estradiol level was <73.4 pmol/L (markedly elevated values were to be expected).

Based on the suspected presence of gonads in the inguinal canal, the patient underwent surgery on her third day of life. Intraoperative vaginoscopy showed no uterine cervix. A gonadal biopsy revealed a fragment of testicular parenchyma consisting of solid cords with Sertoli cells and spermatogonia. Leydig cells were not identified. Left gonad biopsy showed a high number of spermatogonia, a hydatid with a cystic aspect, and many tubular structures consistent with epididymis. A duct consistent with a müllerian remnant was found in the vicinity (Fig. 2). Both testes were replaced into the abdomen.

The karyotype was 46 XY. The molecular study of the AR gene found a base change in exon 5, an arginine by glutamine replacement at codon 752 (R752X). This mutation had previously been reported in the literature in a patient with CAIS,¹ and therefore confirmed the diagnosis. The molecular study of the mother was positive for the same mutation, but she had no phenotypic changes.

CAIS is an X-linked autosomal recessive disease caused by a mutation in AR that may be inherited (70%) or occur de novo (30%). The gene is located in the chromosomal region Xq11-12 and consists of eight exons encoding for a 919 amino acid protein. It has four functional domains: NTD (N-terminal transactivation domain), encoded in exon 1; DBD (DNA binding domain), encoded in exons 2 and 3; a hinge region; and LBD (ligand binding domain), encoded by exons 4–8.² AR is located in cell cytoplasm bound to protein, and upon ligand binding translocates to the nucleus, where it is bound to DNA. The same mutation may cause different phenotypes in the same affected family.³

Prevalence is estimated at 2–5/100,000.⁴ Clinically, CAIS occurs in individuals with karyotype 46 XY and normal external female genitalia, blind-ending vagina, and intra-abdominal testes. Leydig cells secrete testosterone in adequate amounts for a male of that age, which is normally converted into dehydrotestosterone (DHT) through 5- α reductase, but the effect of DHT is virtually nil because of the presence of non-functioning AR. AMH production by Sertoli cells and the synthesis of its receptor AMHR2 is not affected by AR impairment. This allows for a normal action of AMH during the embryonic period, explaining the regression of müllerian structures (upper third of vagina, uterus, and ovaries) in patients with CAIS.

CAIS should be suspected in two instances: firstly, in a phenotypically female newborn with bilateral inguinal hernia, because this is uncommon in females. One to 25% of these lesions correspond to CAIS.⁵ The second presentation form occurs in a female adolescent with adequate breast development and a little or no pubic and/or axillary hair

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