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Intracranial Castleman's disease presenting as hypopituitarism

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Abstract Castleman's disease is an atypical lymphoproliferative disorder that may present as a localized or multicentric form. The involvement of the central nervous system is rare. We describe here a case of Castleman's disease with involvement of the hypothalamus and meninges, presenting as hypopituitarism. Radiological and clinical pathological features are emphasized and a review of the literature is presented.

Introduction

Castleman's disease (CD), also known as angiofollicular or giant lymph node hyperplasia, is an atypical lymphoproliferative disorder that may present as a localized or multicentric form. The former is commonly detected in young patients with a localized tumor, with the possibility of surgical resection and a benign course. The multicentric form tends to occur in older patients and is associated with diffuse adenopathy, extranodal involvement, systemic symptoms and hematological abnormalities. The clinical course of multicentric CD is variable, but the prognosis is often poor [1, 2].

Histologically, CD is characterized by small follicular centers exhibiting prominent central hyalinized vessels. The interfollicular areas show vascular proliferation, with variable numbers of plasma cells and immunoblasts. The quantity of interfollicular plasma cells determines the different types of CD, with histological types including a hyaline vascular form, plasma cell variants, as well as a mixed type [3, 4, 5]. The plasma cell variant, characterized by the presence of significant amounts of mature plasma cells, may be present both as a localized and as a multicentric form, and about one-third of the patients develop either Kaposi sarcoma or B-cell lymphoma [6].

Involvement of the central nervous system (CNS) may be seen in the multicentric form, occasionally affecting the meninges. To the best of our knowledge, few cases of CD with involvement of the CNS have been reported, and none of these previously reported cases affected the hypothalamic region [7, 8, 9, 10. 11].

In the present article, we describe a new case of CD with involvement of the hypothalamus and meninges, with emphasis on radiological and clinical pathological features.

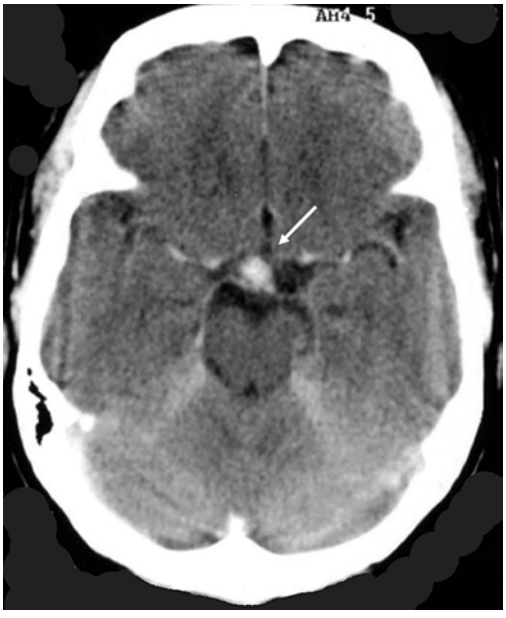

Fig. 1 CT scans showing a suprasellar lesion with contrast enhancement (*arrow*)

Case report

A 40-year-old woman presented with a 2-year history of amenorrhea, weight gain and polyuria. The patient presented high serum levels of sodium, high plasma osmolarity, and low urinary osmolarity, suggesting the diagnosis of diabetes insipidus, which was confirmed after the water deprivation test. Hypothyroidism was diagnosed by low levels of T4 and thyroid-stimulating hormone. In addition, adrenal, growth hormone and gonadotrophic deficiencies were confirmed by dynamic tests, indicating hypothalamic-pituitary dysfunction. Vasopressin (DDAVP), glucocorticoid, and thyroid hormone were replaced to treat hormonal deficiencies. Hematological and biochemical studies were unremarkable. There were no abnormal findings in the clinical and neurological examinations.

In order to determine the etiology of the hypopituitarism, computed tomography (CT) and magnetic resonance imaging (MRI) were performed. CT scans revealed a suprasellar lesion located in the hypothalamic and infundibular regions associated with an intense contrast enhancement (Fig. 1). MRI demonstrated an expanded lesion in the hypothalamus and infundibular regions, measuring 1.6×0.8 mm. The lesion was characterized by an isointense signal in T1- and T2-weighted sequences associated with an intense contrast enhancement by gadolinium-DTPA contrast (Fig. 2). Meningeal enhancement could be seen in the tentorium and right fronto-temporo-parietal regions (Fig. 2).

Surgical treatment was considered, but total removal was not attempted because of the lesion extension. Therefore, the patient was submitted to an open biopsy of the meningeal lesion in the right frontoparietal area. The lesion was related to the arachnoid membrane and easily dissected from the brain surface.

Microscopic examination disclosed dense thickness of the arachnoid membrane that exhibited a diffuse population of lymphoid cells intermingled with small follicles with expanded mantle zones and well-defined germinal centers. It was noteworthy that the follicular centers

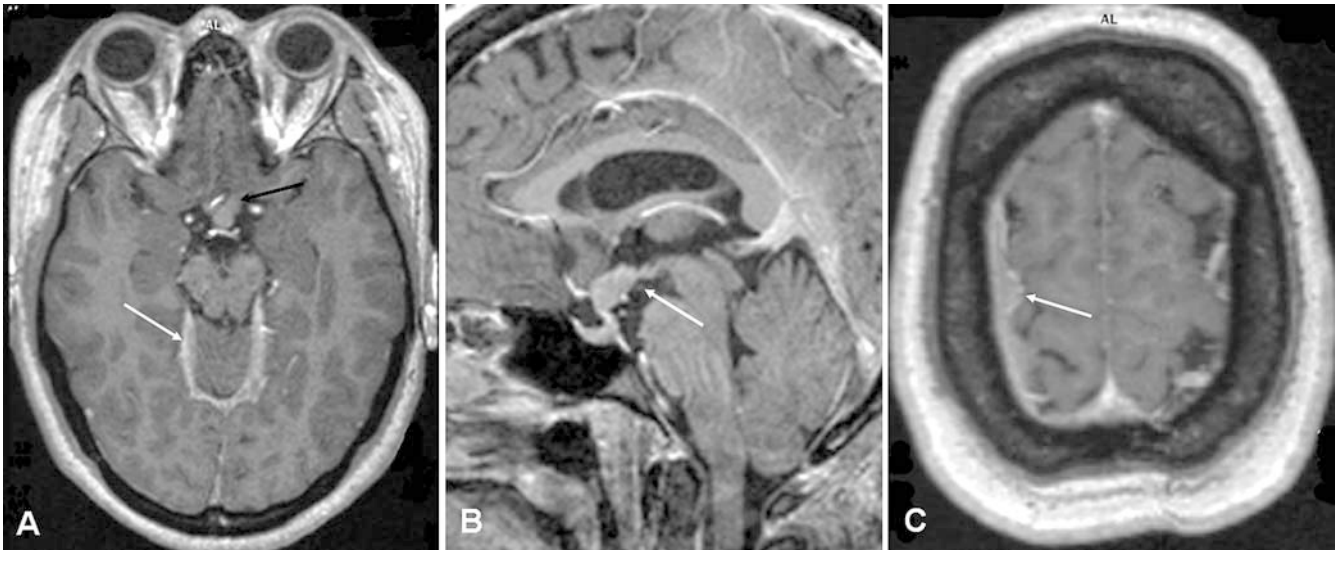

Fig. 2 **A** An axial T1-weighted image showing the suprasellar lesion (*black arrow*) with an intense contrast enhancement. Contrast enhancement is also seen in the tentorium region (*white arrow*); **B** a sagittal T1-weighted image with contrast enhancement demonstrates in detail the location of the hypothalamic and infundibular lesion (*white arrow*); **C** an axial T1-weighted image with contrast shows meningeal enhancement in the right frontoparietal areas (*white arrow*)

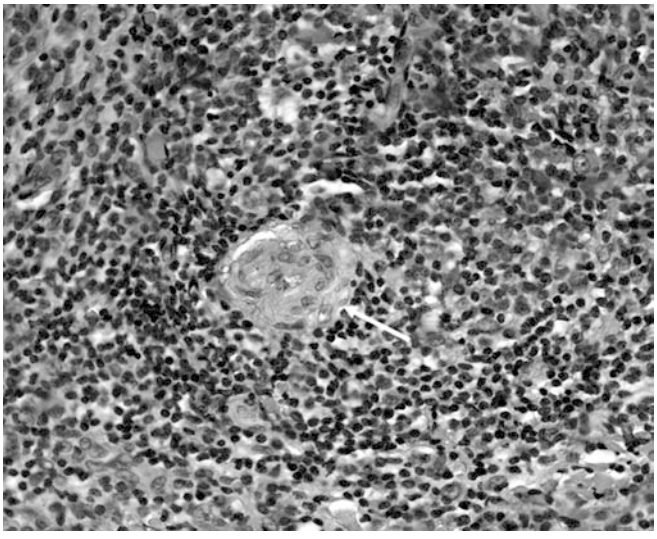

Fig. 3 Histological features. Note the presence of typical hyalinized vessels (*arrow*) with mature perivascular lymphocytes. (HE, 400×)

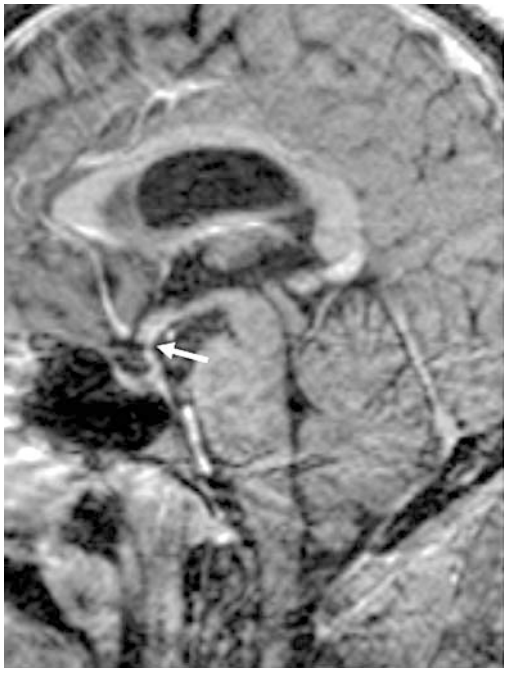

Fig. 4 After 3 months of steroid therapy, a sagittal contrast-enhancement T1-weighted image demonstrates a significant reduction of the hypothalamic and infundibular lesion (*arrow*)

exhibited prominent central vessels with hyalinized walls and proliferating endothelial cells (Fig. 3). The interfollicular area showed numerous plasma cells and immunoblasts. In the immunohistochemical study, most lymphoid cells showed immunoreactivity for CD20 in addition to CD3. Kappa and lambda immunostains demonstrated a polyclonal cell population within germinal centers. CD30, CD15, Bcl-2 and EMA tests were performed to exclude the diagnosis of Hodgkin's lymphoma, follicular lymphoma and lymphoplasmocyte-rich meningioma. Thus, the final diagnosis was Castleman's disease, plasma cell variant (Fig. 3).

The patient was subjected to an extended protocol of investigation, including ultrasound (US) of the abdomen, chest X-ray, CT scans of the neck, chest, abdomen and pelvis, myelogram, gamma globulin levels, rheumatoid factor, antinuclear antibody and tumor markers—carcinoembryonic antigen (CEA), cancer antigen 125 (CA-125) and human chorionic gonadotropin (B-HCG)—as well as Bence Jones protein and anti-HIV enzyme-linked immunosorbent assay. All of these exams were within normal limits. The study of cerebrospinal fluid (CSF) revealed 12 cells per mm^3 with 92% lymphocytes and 8% monocytes, 31 mg% of total protein and 54 mg% of glucose, with negative tests for HIV, fungi, Venereal Disease Research Laboratories (VDRL) test, neurocysticercosis and tuberculosis.

Steroid therapy with 2 mg/kg/day prednisone for 30 days was applied for the clinical treatment. Three months after steroid therapy, a control MRI was performed, demonstrating a significant reduction of the hypothalamic and infundibular lesion, and also contrast enhancement of the meninges (Fig. 4). The patient has been in good clinical condition, receiving DDAVP and thyroid hormone replacement therapy.

Discussion

Although CD was initially described as a solitary lesion in the mediastinum [1]—the most common site of involvement—it has been reported to occur at many other locations, such as the abdominal cavity, pulmonary parenchyma, neck, axillary regions, and skeletal muscle [2, 12]. The involvement of the CNS has been described as one of the manifestations of systemic CD [3, 8, 10], and as a solitary form has only rarely been reported [7, 9]. Isolated CNS disease behaves in a manner similar to its extracranial, unifocal counterparts, with good outcomes seen over the short follow-up periods reported [7].

Analysis of immunoglobulin rearrangements and immunohistochemical studies of the plasma cell variant have demonstrated that CD is a polyclonal lymphoid hyperplasia [12]. However, the pathogenesis of CD is unknown, and several pathogenetic mechanisms such as chronic inflammation [13, 14] immunodeficiency [6], and a myriad of infectious agents have been proposed [14]. Some reports have suggested a pivotal role of interleukin (IL)-6 in the pathogenesis of this syndrome, since lymph nodes from patients with CD excrete large amounts of this cytokine. IL-6 is a soluble protein necessary for the

proliferation and maturation of B-lymphocytes into immunoglobulin-secreting plasma cells. Also, IL-6 induces proliferation of normal endothelial cells [15] and appears to correlate with systemic manifestations of the disease [16]. Interestingly, the multicentric form of CD is associated with a human herpes virus infection (HHV-8) [6] that encodes a functional analogue of IL-6. HHV-8 is also associated with AIDS and AIDS-related Kaposi's sarcoma (KS), which may explain the development of KS in patients with CD who do not have HIV infection [2].

The previously reported cases of intracranial CD usually showed a meningeal involvement, manifested by contrast enhancement of this area with or without mass effect. A presumptive radiological diagnosis of meningioma is usually made. Differential diagnoses for lesions mimicking meningiomas include several pathologies, such as solitary fibrous tumors, hemangiopericytomas, gliosarcomas, leiomyosarcomas, melanocytoma, metastatic carcinomas, metastatic leiomyosarcomas, Hodgkin's disease, plasmocytomas, Rosai-Dorfman disease, neurosarcoidosis, plasma cell granulomas, xanthomas, rheumatoid nodules, and tuberculomas. The knowledge of these lesions may facilitate their recognition intraoperatively, including changes in the surgical approach, and the treatment in the postoperative period [3, 8, 10, 11].

Additionally, the involvement of the hypothalamic area and pituitary gland by a non-primary tumoral or vascular lesion is a rare condition [17]. However, granulomatous diseases such as tuberculosis and sarcoidosis, tumoral infiltrative lesions such as lymphoma, histiocytosis and other lymphoproliferative conditions and autoimmune diseases might involve the hypothalamic area and/or pituitary gland [17]. The radiological images in these cases are not diagnostic. Thus, in most patients, MRI by itself does not provide the precise distinction between these disease subgroups.

We suggest that CD should be considered as an uncommon etiology in the differential diagnosis of an infiltrative, expanded and contrast-enhancement lesion affecting the hypothalamic and infundibular regions, particularly when associated with meningeal involvement.

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