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Case report

Parotid gland involvement in Heerfordt syndrome: a case report

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Key words

Sarcoidosis • Granuloma • Parotid • Heerfordt syndrome

Summary

Sarcoidosis is a multisystemic granulomatous disease characterized by the presence of noncaseating granulomas, the exact etiology of which is yet to be determined. Most of patients show granulomas located in the lungs or in the related lymph nodes. However, lesions can affect any organ.
Noncaseating granulomas are not a pathognomonic sign of sarcoidosis, being observed also in other diseases, therefore the diagnosis is often of exclusion.
We report a case of sarcoidosis with parotid gland involvement in the context of a Heerfordt syndrome, discussing about its clinical presentation, pathogenesis, pathology and differential diagnosis with other granulomatous diseases.

Introduction

Sarcoidosis is a systemic disorder of unknown cause, pathologically characterized by the accumulation of inflammatory cells forming non-caseating granulomas. Lesions can be localized in any organ but in about 90% of patients, granulomas affect the lungs or the related lymph nodes.
Extra-pulmonary sarcoidosis has been described in 30% of patients with the disease [1]. The most common sites are liver, spleen, biliary tree, peritoneum, and abdominal lymphonodes [2]. A cutaneous and ocular involvement is reported in 25% of patients.
Heerfordt syndrome, first described in 1909 [3] as part of the spectrum of sarcoidosis, occurs in approximately 0.3% of all sarcoidosis cases [4]. It is defined as a combination of uveitis, parotid gland enlargement, fever and facial nerve palsy [5] Dr. Jan Waldenström made the observation that this syndrome was associated with sarcoidosis in 1937 [6]. Cases presenting all the abovementioned features are defined as "complete Heerfordt syndrome", nevertheless this syndrome manifests in various forms, and cases of complete Heerfordt syndrome are extremely rare [1 7].
We herein report a case of parotid gland involvement of sarcoidosis in a woman with Heerfordt syndrome presenting with the entire constellation of symptoms.

Case report

A 60 years old woman was admitted to the neurological clinic of our department for the sudden appearance of blurred vision, headache and mouth deviation to the left, since a week, after a febrile episode. The day after fever appearance, she showed a complete facial palsy and a bilateral enlargement of the cheeks. Physical examination revealed unpainful enlargement of the left parotid gland and bilateral facial palsy. She also presented left abducent nerve palsy with limitation of the lateral movements of the eye, and deviation of the tongue to the left. No skin rashes were noted. The remaining neurological examination was normal. Infectivological screening, anti-neuronal, anti-ganglioside and anti-myelin antibodies were all negative. The cerebrospinal fluid examination excluded the presence of inflammatory or infective diseases. An ophthalmologic evaluation revealed bilateral vascular sclerosis and alterations compatible with the diagnosis of uveitis. Brain Magnetic Resonance Imaging (MRI) with gadolinium showed the presence of contrast enhancement of both the internal auditory canals with bilateral involvement of VII cranial nerve (Fig. 1A) and impregnation of the cisternal portion of the left abducent nerve (Fig. 1B). The MRI of the parotid glands (Fig. 2) showed three nodular lesions in the left parotid gland

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Fig. 1. Brain MRI of the patient showing contrast enhancement of both the internal auditory canals with bilateral involvement of VII cranial nerve (A) and of the cisternal portion of the left abducent nerve (B).

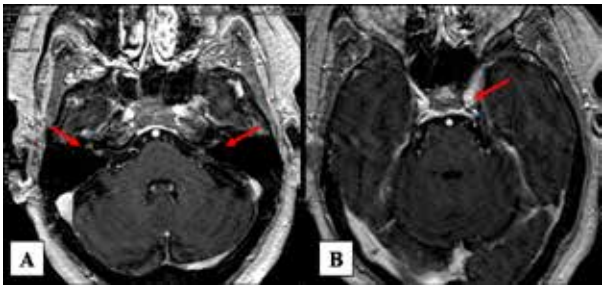


Fig. 2. MRI showing three nodular areas in the right parotid gland and a smaller lesion in the left parotid gland with hyperintense signal in T2-weighted images, hyperintense signal in T1 acquisitions and homogeneous contrast enhancement.

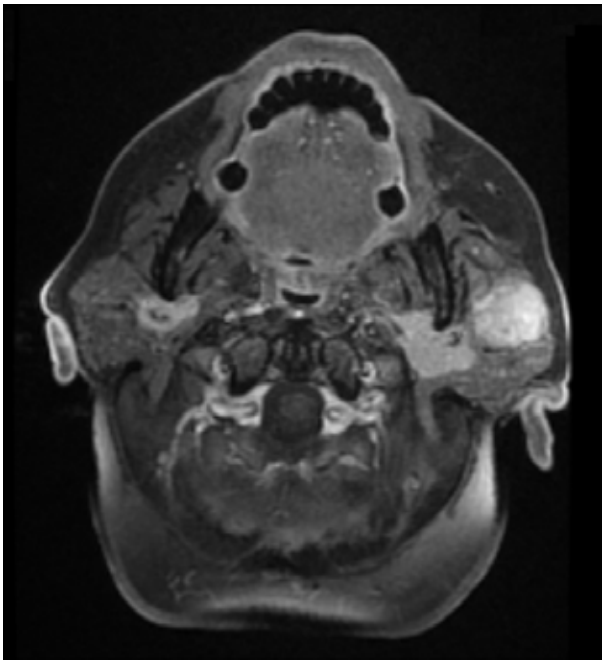


Fig. 3. CT scan showing diffuse areas of parenchymal consolidation with "frosted glass" areas in both lungs (A); increased dimensions lymph nodes were present in mediastinal stations (B).

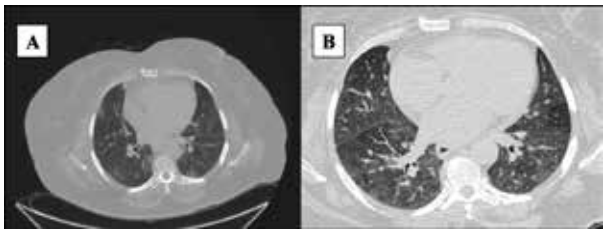


Fig. 4. Histological examination revealed areas of chronic granulomatous inflammation with non-necrotizing epithelioid cell granulomas, in the context of parotid gland.

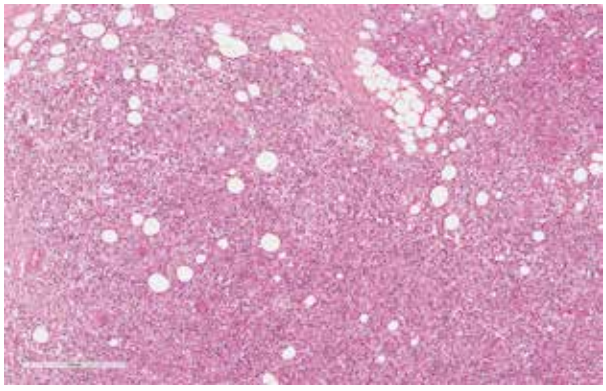
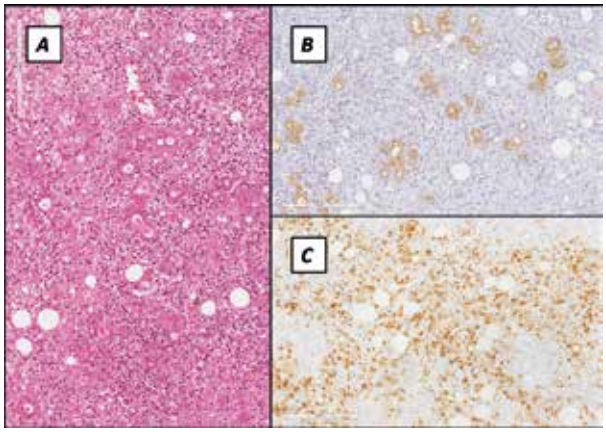


Fig. 5. Granulomas showed epithelioid histiocytes, foreign body-type multinucleated giant cells and some lymphocytes (A); immunostaining for pan-CK (B) and CD68 (C) confirmed the presence of residual glandular ducts and the histiocytic phenotype of epithelioid cells



and an area of altered signal in the right parotid gland. Chest CT scan revealed diffuse areas of parenchymal consolidation with "frosted glass" areas in both lungs (Fig. 3A) and mediastinal lymph nodes of increased dimensions (Fig. 3B). Serum ACE enzyme levels were within the normal range. Nevertheless, a fibrobronchoscopy was performed with bronchoalveolar lavage. The cytological analysis showed lymphocytosis (lymphocytes: 16%; normal value: 2-12%). Lymphocyte typing revealed an increased CD4/CD8 ratio with a value greater than 3.6 (positive predictive value of 76% with 94% specificity) suggesting the diagnosis of sarcoidosis. In order to confirm the diagnosis, a biopsy of the left parotid gland was performed. Histological examination of hematoxylin and eosin-stained sections (4-5 micron thick) revealed, within the context of normal salivary gland, an area of chronic granulomatous inflammation with marginated, non-necrotizing, epithelioid cell nodules (Fig. 4). Granulomas showed epithelioid histiocytes, foreign body-type multinucleated giant cells (Fig. 5A), asteroid bodies, and a few lymphocytes. Cytokeratins immunostaining (pan-CK and CK7) revealed residual glandular ducts and acini within the granulomatous inflammatory area (Fig. 5B). Immunohistochemical staining for CD68

confirmed the histiocytic phenotype of epithelioid cells (Fig 5C). Finally, the morphological and immunohistochemical findings of the lesions were consistent with the parotid gland localization of sarcoidosis leading to the diagnosis of Heerfordt syndrome. Treatment with oral prednisolone at the dose of 60 mg per day, after a three months follow up, led to a moderate clinical and radiological improvement.

Discussion

Heerfordt syndrome is a rare disease, not common in the Western countries, therefore clinical and pathological diagnosis could be missed. The classical clinical tetrad of facial nerve palsy, parotid gland enlargement, anterior uveitis and fever can be partially present with one symptom missing or prevailing on others [6-8]. The incidence of cranial nerve palsy in sarcoidosis is about 5-6% with the facial nerve followed by the optic nerve being the most common nerves involved. Both the etiology and the pathogenesis of this syndrome are still ambiguous. Nerve root and cranial nerve involvement can be either caused by the compressive effect of an adjacent granuloma or due to perivascular and intraneural lymphocytic infiltration. In cases of a granulomatous sialadenitis, particular care should be taken to distinguish the diagnosis of sarcoidosis from other diseases such as tubercolosis, atypical mycobacterial infections, protozoan and fungal infections, no immune-mediated granulomas (typically represented by foreign-body granulomas), granulomatous reactions linked to neoplasms, lymphomas, Wegener's Granulomatosis, Sjögren's syndrome, cat-scratch disease, calculus or carcinomatous duct obstructions or orofacial granuloma [9]. In a clinicopathological study of 57 cases of granulomatous sialadenitis of the major salivary glands, the authors reported that tubercolosis, sarcoidosis, calculous duct obstruction and carcinomatous duct obstruction were the most frequent causes of granulomatous sialadenitis; in particular, this study referred calculus sialadenopathy as a major cause of granulomatous sialadenitis [10]. Histologically, tubercolosis as well as fungal infections, differs from sarcoidosis for the presence of a central caseating-necrosis area within the granuloma; however, tubercolosis, especially in the early stages of the disease, can show the presence of small non-caseating epithelioid cell granulomas. Sarcoid granulomas can also contain focal central necrosis areas, so histochemical staining and molecular biology techniques can be very useful in the differential diagnosis, allowing the identification of etiologic agents within the inflammatory tissue [11]. Furthermore, it needs to be pointed out the presence of the so-called "Necrotizing sarcoid granulomatosis (NSG)", a rare systemic disease, characterized by sarcoid-like granuloma, vasculitis and variable degrees of necrosis. Cases of gland duct obstruction often show single to multiple small granulomas which contain mucin and are related to ruptured ducts [10]. In cat-scratch disease, as well as in atypical mycobacterial infections, granulomas show suppurative necrosis central areas and the evidence of etiological agent can be obtained through histochemical staining and molecular biology [12]. Wegener's granulomatosis is generally characterized by less demarcated granulomas than sarcoid or tubercular ones [13]. In conclusion, since the histological presence of non-caseating epithelioid cell granuloma is not a pathognomonic sign of the disease, histological diagnosis of sarcoidosis is often made based on the integration of morphological, immunohistochemical, histochemical, clinical and radiological data [14]. In our case, the evidence of sarcoid granulomas on parotid gland biopsies, together with classical clinical tetrad of facial nerve palsy, parotid gland enlargement, anterior uveitis and fever, helped us to make a diagnosis of parotid gland localization of sarcoidosis as part of Heerfordt syndrome.

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