

## Case Report

# Adrenal Castleman disease associated with paraneoplastic pemphigus: a case report and literature review

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**Abstract:** Castleman tumor, a rare lymphoproliferative disorder, is one of the associated tumors in paraneoplastic pemphigus (PNP). Castleman tumor was a frequently reported neoplasm in association with paraneoplastic pemphigus which was caused by an autoimmune reaction originating from the B lymphocytes. Castleman tumor association with PNP is a rarely reported subtype of PNP in China. Early detection and removal of the tumor are crucial for the treatment of tumor-associated autoimmune disease. Here we described a case of a patient with PNP associated Castleman tumor in order to clearly understand and improve the prognosis of the disease. Pathologic evidence proved that it was the follicular dendritic cell sarcoma-like Castleman tumor.

**Keywords:** Castleman disease, adrenal tumor, paraneoplastic pemphigus, autoimmune disease, prognosis

### Introduction

Castleman's disease (CD), first described by Castleman in 1956, is an uncommon and poorly understood disorder of lymph node hyperplasia with unknown etiology [1]. Castleman tumor is a distinct lymphoproliferative disorder of uncertain origin [2]. Histologically, it is characterized by extensive vascular proliferation with surrounding abnormal lymphoid follicles. Paraneoplastic pemphigus (PNP) is an autoimmune blistering and erosive mucocutaneous disease associated with neoplasia, most commonly of lymphoreticular origin [3]. The disease is a paraneoplastic autoimmune multiorgan syndrome characterized by distinctive clinical symptoms and signs, such as severe, painful mucosal erosions, polymorphous skin lesions, histopathologic hallmarks, and immunologic findings [4]. One of the characteristic features of PNP associated CD and other benign tumors is the remarkable improvement in symptoms noted after removal of the tumor [2].

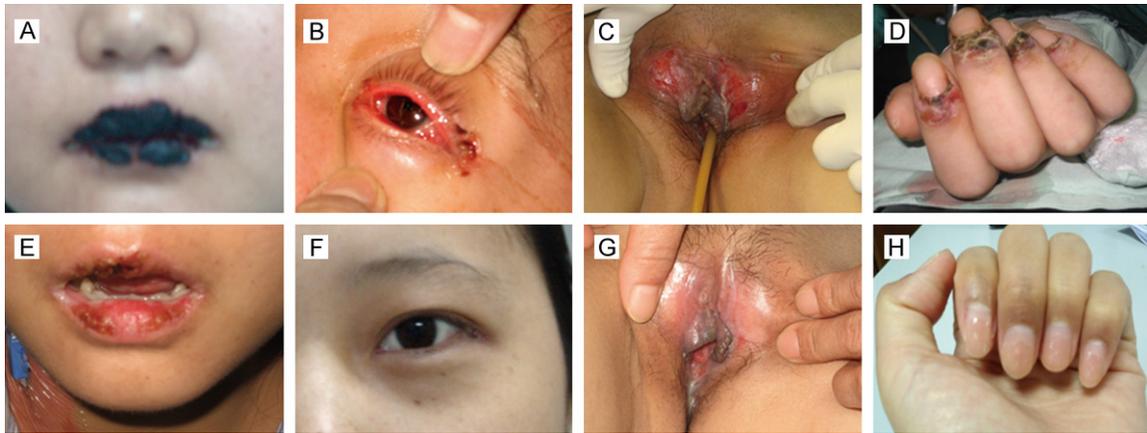
To better understand Castleman tumor associated with PNP, we presented a rare but clinically

typical case of adrenal CD associated with PNP with review of the related literatures.

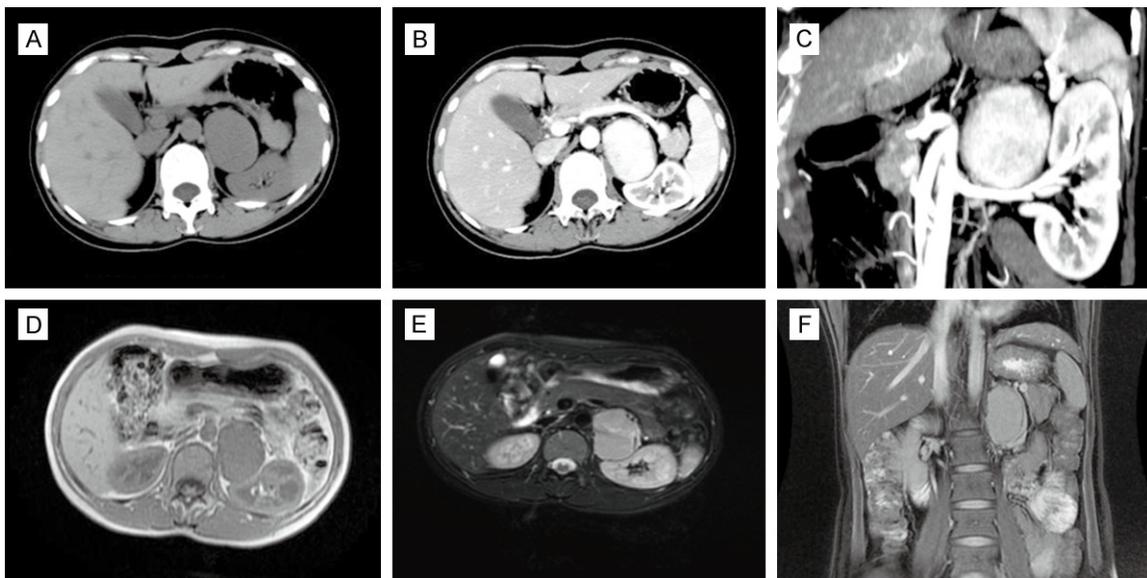
### Case presentation

A 22-year-old female admitted to our hospital on August 29, 2008 because of 2-month vulvae itching with much yellowish vaginal discharge accompanied by persistent painful oral erosions. Vulval erosions were also seen on the labia majora. Corticosteroids and antibiotic therapy was given in other hospitals, but no improvement was observed. Then she presented with extensive erosions of the oral mucosa, tongue, lips, fingers and palms and a 2-week history of lichenoid papules, symmetrically distributed on the trunk and extremities. Later she felt uncomfortable on her left eye with conjunctival congestion (**Figure 1A-D**). She lost 5 kg of her body weight mainly due to very little food intake. Physical examination revealed no peripheral lymphadenectasis and no significant abnormality. The white blood cell counts were high ( $12.9 \times 10^9/L$ ) and the serum IgG level was elevated (2140 mg/dl). Other laboratory tests and tumor markers were within the nor-

## Adrenal Castleman disease with paraneoplastic pemphigus



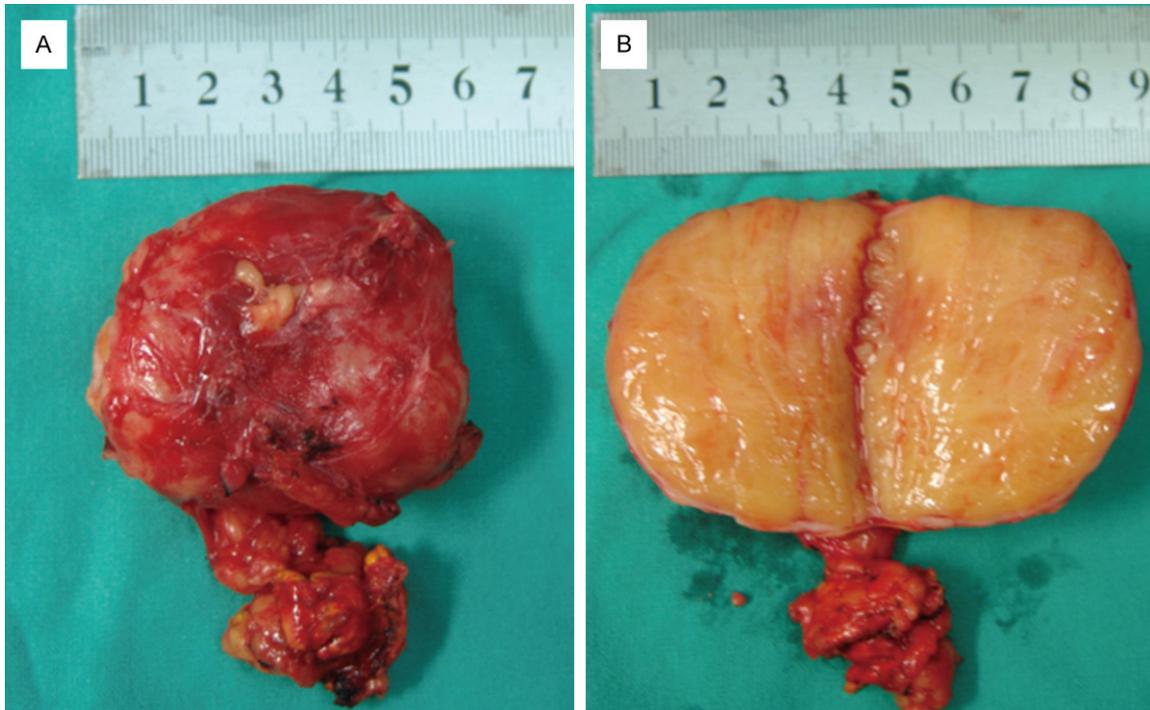
**Figure 1.** Mucosal manifestations of the patient with PNP. A: Violet lesion with hemorrhagic crusting on the lips. B: Conjunctival congestion on her left eye. C: Erosions on the labia majora. D: Severe erosions and crusts on the fingers. E: Improved lesion on the lips after resection of the tumor. F: Cured conjunctival congestion after resection of the tumor. G: Healed erosions on the labia majora after resection of the tumor. H: Recovered erosions on the fingers after resection of the tumor.



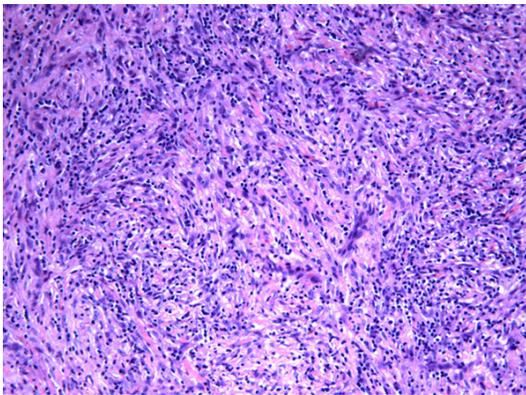
**Figure 2.** CT and MR imaging features of a retroperitoneal location in association with PNP. A: CT scan shows a well-circumscribed, homogeneous mass in the left suprarenal space. B: The tumor was enhanced after intravenous injection of iodinated contrast agent, with similar CT value the great vessels in this circumstance. C: The tumor was also clearly showed on coronal image. D: Axial gradient-echo T1-weighted image shows that the mass is hypointense to liver and it appears to be separate from the left kidney and the cauda pancreatic. E: On an axial spin-echo T2-weighted image, the mass is more intense than liver but less intense than vertebral body. The signal is homogeneous with focal hypointense areas. F: On a coronal 2D FS FIESTA the tumor appears to be separate from the left kidney.

mal range. Histological examination of her oral mucosa showed intraepidermal acantholytic blisters or bullae. A diagnosis of PNP was made and ultrasonography revealed a well-circumscribed hypoechoic mass over the medial aspect

of the left suprarenal area. CT scan showed a 54 mm\*46 mm\*31 mm mass in the left retroperitoneal area, rounded, well circumscribed, uniformly hypodense with some small calcifications but no cystic or fatty areas (**Figure 2**).



**Figure 3.** The specimen of the tumor. A: Resected tumor (50 mm\*50 mm\*30 mm) from showed very similar to a huge lymph node with a fishlike appearance. B: The cut surface showed to yellow color and fleshy appearance.



**Figure 4.** Histological section of the tumor: Histologic section of the resected tumor shows a Castleman tumor of hyaline vascular type: the normal structure of the lymph node was effaced and replaced by numerous small follicular centers with prominent central vessels, which exhibited hyalinized walls and prolific endothelial cells. The small follicular centers were surrounded by concentric layers of follicle center cells. The interfollicular areas showed vascular proliferation and variable numbers of plasma cells. (Hematoxylin-eosin, original magnification\*100).

A laparotomy was performed; during the operation, a yellow mass was located below the left adrenal gland, upon the left kidney, and lateral

to the abdominal aorta. Extensive resection of the mass was performed and one well-capsulated mass 50 mm\*50 mm\*30 mm in size and about 80 g in weight was resected. Macroscopically, the tumor was a solitary mass with relatively intact and smooth capsules. The cut surface showed yellow color and fleshy appearance (**Figure 3**). Pathological examination showed histological features of the hyaline-vascular type with tumor-like proliferation of follicular dendritic cell (FDC) (**Figure 4**). Immunohistochemistry staining revealed the tumor cells had a CD3<sup>+</sup>, CD43<sup>+</sup> and Actin-positive phenotype. A diagnosis of adrenal Castleman disease was made according to the pathological finding and immunohistochemistry.

After resection of the Castleman's tumor, cutaneous lesions improved gradually and disappeared within 3 weeks and erosions of the mucosa and ulcers also improved (**Figure 1E-H**). However, erosions and shallow ulcers in the oral cavity and on the tongue were recovered comparatively slowly. During the five-year follow-up, she completely recovered from cutaneous lesions and achieved significant improvement of mucosal involvement.

### Discussion

CD is a rare heterogeneous lymphoproliferative disorder with unknown etiology and pathogenesis. The most common locations are the thorax (63%), abdomen (11%) and axilla (4%). It is infrequently associated with various immunological abnormalities or subsequent development of malignancy such as Kaposi's sarcoma, malignant lymphoma and plasmacytoma.

Two clinical types (localized and multicentric) and three histological variants (hyaline vascular, plasma cell and mixed) of CD have been described. Localized disease manifests as a solitary mass, which may be well circumscribed or infiltrative. It is associated with lymphadenopathy confined to one lymph node or nodal area [5], and usually follows a benign course. Multicentric disease carries a worse prognosis, and subsequent infection or malignancy may lead to death [5]. The hyaline-vascular variety accounts for up to 90% of CD and is usually asymptomatic; the plasma cell subtype is less common, and 50% of these patients experience anemia, fever, fatigue, hyperglobulinemia and hypoalbuminemia [6]. The disease may occur in almost any area where lymph nodes are normally found. CD with a suprarenal localization, mimicking an adrenal tumor, is rare, as reflected by the small number of case reports that have been documented. Here we presented a rare case of unicentric CD of the hyaline-vascular type with a left suprarenal location that mimicked an adrenal neoplasm.

PNP was defined in 1990 by Anhalt [3] according to clinical, histological, direct and indirect immunofluorescence, and immunoprecipitation criteria. The most commonly associated neoplasm in PNP is non-Hodgkin lymphoma (42%). Others are chronic lymphocytic leukemia (29%), Castleman tumor (10%), thymoma (6%), retroperitoneal sarcomas (6%), and Waldenström macroglobulinemia (6%) [2, 3]. Presumably, direct stimulation by the antigens coming from the digestive and urinary-reproductive tracts was also involved in the pathogenesis of PNP in association with Castleman tumors. The presence of the tumor is thought to cause immune disturbances which lead to an auto-aggressive epithelial reaction.

PNP seems to be an autoantibody-mediated mucocutaneous disorder. But, how do Castle-

man's tumors in these patients stimulate the production of autoantibody? One hypothesis is that the tumor proteins function as antigens and induce the development of autoantibody against epithelial proteins [7]. There is also no direct evidence that Castleman's tumors alter the response of antibody synthesis in the immune system via tumorigenic cytokines or helper T cells [8]. The epitope spreading hypothesis suggests that lichenoid dermatitis initiates primary autoimmune responses by the release of intracellular antigens from keratocyte necrosis [9].

Imaging exams such as ultrasound and CT or MRI cannot identify CD due to the lack of tumor-specific signs, but these exams show important information about the exact tumor location. Only surgical resection and histological evaluation give an accurate characterization of this tumor.

As for the mechanisms by which CD induces PNP, it has been proposed that autoantibodies secreted from the Castleman tumor itself may play a pivotal role [10]. Ashinoff *et al.* [11] postulated that possible expression of foreign tumor antigens that cross-react with epidermal antigens induce the autoreactive clones of T lymphocytes. Anhalt speculated that tumors associated with PNP may produce plakin proteins that result in initiation of autoimmune responses. Other investigators believed that the autoimmune reaction was related to the epitope spreading [11, 12]. Immunoglobulin G was found in the cell culture medium and can recognize the specific antigens in epithelia [11]. Recently, rearranged immunoglobulin heavy and light-chain variable region genes were cloned and their sequences were analyzed in Castleman tumors associated with PNP. A high incidence of somatic mutations in complementarity-determining regions and framework regions was observed in the cloned variable region of heavy-chain and light-chain genes. These clones were found to have experienced switch recombination and have the structural basis to produce autoantibodies. In this series of patients, IgG antibodies in the cell culture media were found to recognize the recombinant envoplakin, periplakin, and desmoplakin fusion proteins, which are believed to be the specific target antigens of PNP. Therefore, we believe that the autoantibodies are directly pro-

duced by the cells in the Castleman tumor. Because the autoantibodies originated from the Castleman tumor, the early detection and removal of the tumor is essential for the treatment of this tumor associated autoimmune syndrome.

Treatment of localized CD usually involves resection, with excellent long-term results [13]. Radiotherapy has also been reported to be effective in some patients with unicentric disease and is considered a treatment option for patients who are poor surgical candidates or have undergone incomplete resection [13]. Patients with multicentric CD do not benefit from surgical treatment and should be candidates for steroid treatment, with or without chemotherapy [5, 13]. Early removal of the castleman tumor has been proved to be the most important management for the disease. If Castleman tumor is detected, total resection of the tumor is the only way to achieve complete resolution of the disease. As we have stated, intravenous administration of immunoglobulin is recommended before and during the operation. During the operation it is important to block the blood supply to the tumor as soon as possible and avoid squeezing the tumor.

As previously reported [9], our findings indicated a close relation between the presence of a Castleman's tumor and the mucocutaneous manifestations seen in patient with PNP, which did not respond to routine immunosuppressive treatment but were resolved rapidly after resection of the tumor. Our patient showed poor response to corticosteroids, immunosuppressive drugs, and intravenous administration of immunoglobulin. However, she completely recovered from cutaneous lesions and had great improvement of mucosal involvement 3 weeks after operation. The early detection and resection are essential for the treatment of the disease.

### Disclosure of conflict of interest

None.

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