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One Rare Case of Paraneoplastic Pemphigus Associated with Dedifferentiated Liposarcoma

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Abstract

Paraneoplastic pemphigus (PNP) is a rare but life-threatening autoimmune disease often associated with malignant neoplasms, most commonly hematological malignancies. We reported a rare case of PNP associated with dedifferentiated liposarcoma (DDL) of the mediastinum responsive to desmoglein 1 (Dsg1) and desmoglein 3 (Dsg3). Based on mediastinal tumors, severe oral and lip mucosal erosion, systemic pleomorphic rash and circulating anti-desmoglein 1(+) and anti-desmoglein 3(+) antibodies, PNP associated with DDL was established. Antitumor, immunosuppressive and anti-infective agents were given for the therapy. Unfortunately, the patient's clinical symptoms did not improve significantly with the use of intravenous immunoglobulin (IVIG), adequate methylprednisolone, immunosuppression for the PNP, and broad-spectrum antibiotic therapy for his lung infection. When patients with DDL or other malignancies develop pleomorphic skin lesions, the possibility of PNP should be considered. We should try our best to avoid misdiagnosis to save the lives of patients because of the polymorphism of skin lesions.

Keywords: Paraneoplastic Pemphigus; Dedifferentiated Liposarcoma; Mucosal Erosion; Systemic Pleomorphic Rash; Mediastinal Tumor

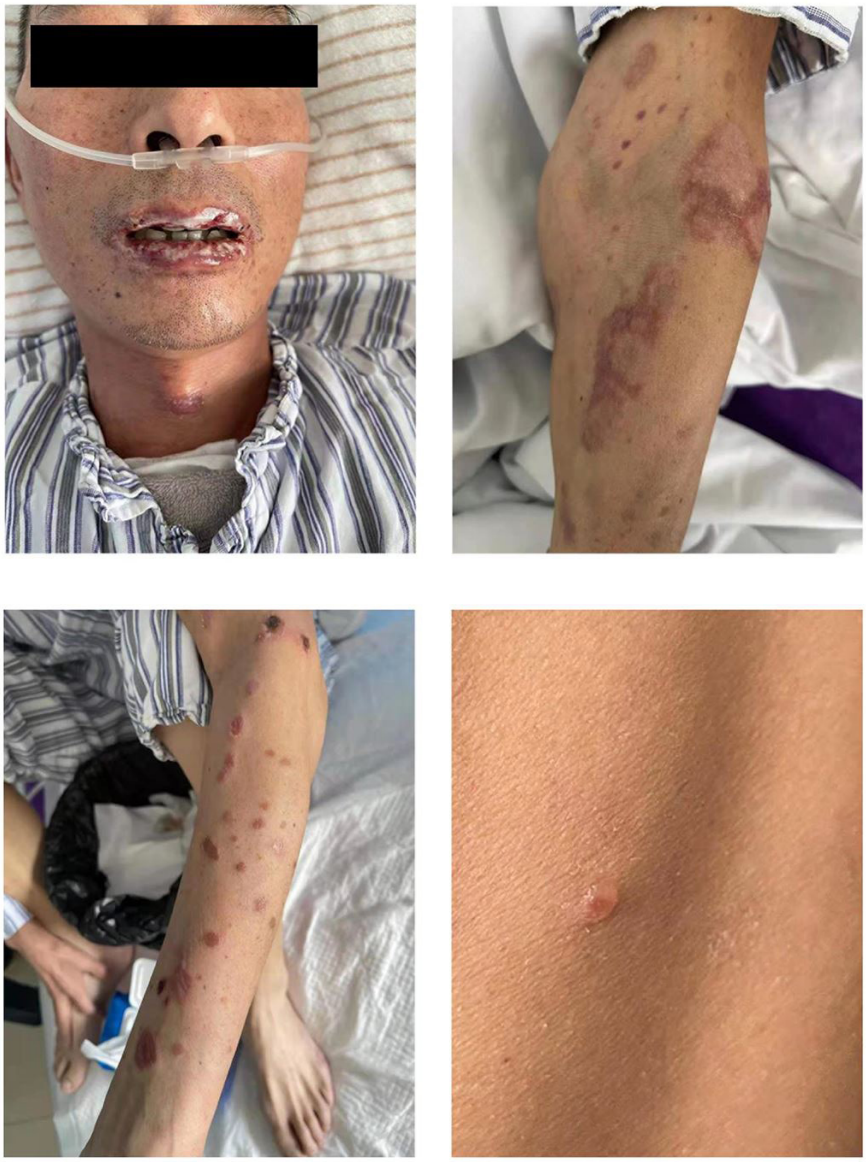
Background

Paraneoplastic pemphigus (PNP) is a rare but life-threatening autoimmune disease often associated with malignant neoplasms, most commonly hematological malignancies, including Castleman's disease, lymphoma, and leukemia [1]. Dedifferentiated liposarcoma (DDL) is a high-grade form of liposarcoma (LPS) that behaves in a more aggressive way [2]. PNP associated with DDL is very rare. We report a rare case of PNP with DDL based on clinical, radiological, and histological findings.

Case Report

A 50-year-old man, was admitted to our stomatology department with a one-month history of refractory oral ulcers and hemorrhagic crusting associated with significant weight loss. Before the appearance of his mucositis, the patient presented with left chest pain. An initial examination revealed a mediastinal mass and lung infection. He noted that within a month, liquid-filled blisters appeared in the arms, neck and back, which were filled with clear liquid and were related to itching (Figure 1). He was initially diagnosed with drug-induced stomatitis as a result of medication history for his lung infection. There was no obvious personal or family history of autoimmune diseases but hypertension and diabetes.

Physical examination revealed oral mucosal erosion, intraoral pseudomembrane with fungal changes, local large areas of erosion, congestion and edema. Skin lesions showed polymorphism, including bullous erosion and ulceration, mainly in the upper limbs, neck and back.



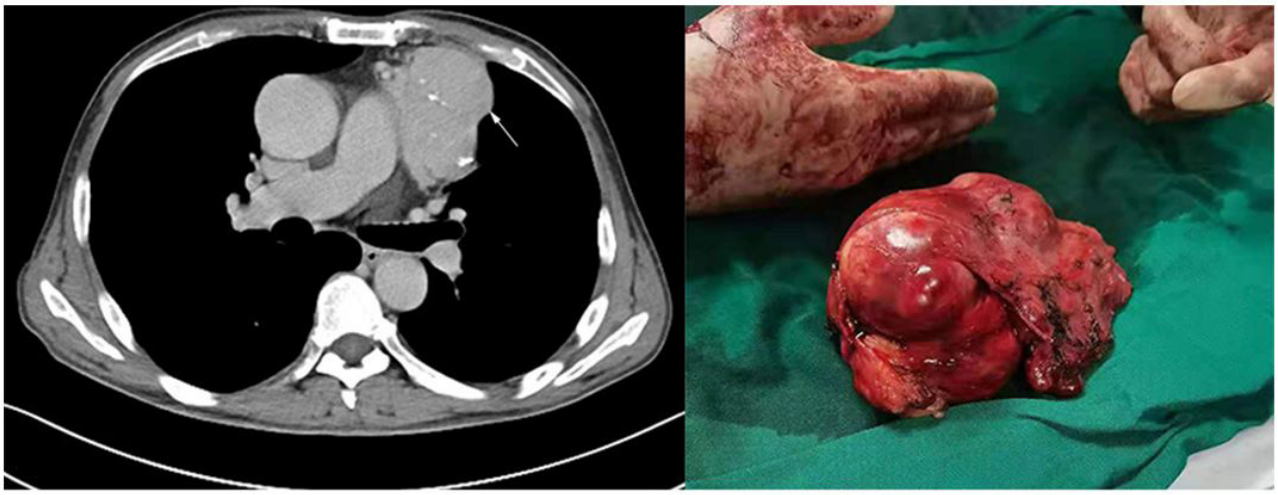
Figuire 1: Mucosal and cutaneous physical examination findings

A plain computed tomography (CT) scan of the chest showed a soft tissue mass (5.78 cm×7.41 cm) with calcification on the left margin of the anterior mediastinum (Figure 2). After contrast enhancement, the mass showed obvious heterogeneous enhancement. There was pericardial/pleural effusion. No metabolically active lesions were discovered elsewhere. The patient was directed to the thoracic surgery department for Surgical exploration and tumour reduction.

Subsequently, the patient underwent mediastinal tumor resection with a solid mass (10 cm×8 cm×6 cm) in the anterior mediastinum (Figure 2). Initially, immunohistochemical stain revealed malignant cells positive for CD31 and CD34, but negative for S-100, HMB45, and Desmin, suggesting angiosarcoma as a possibility (Figure 3). A subsequent molecular detection was amplification of the murine double minute 2 (MDM2) gene, which favor the final diagnosis of DDL. After surgery, the patient was transferred to dermatology for further treatment because of the aggravation of oral and skin lesions.

In the clinical context of mediastinal tumors, severe oral and lip mucosal erosion.

systemic pleomorphic rash and circulating anti-desmoglein 1(+), anti-desmoglein 3(+) antibodies, and bullous pemphigoid antigen 180 (-), PNP associated with DDL was established, which met the diagnosis criteria by Camisa and Helm [3]. After starting intravenous immunoglobulin 20 g for 3 days, he was treated with intravenous methylprednisolone (1 mg/kg) and oral thalidomide 50 mg once a day for the PNP. Eventually, the patient was transferred to the oncology department for further treatment. Later, due to the COVID-19 pandemic, follow-up could not be carried out.



Figuire 2: CT image and clinical picture of the mediastinal mass

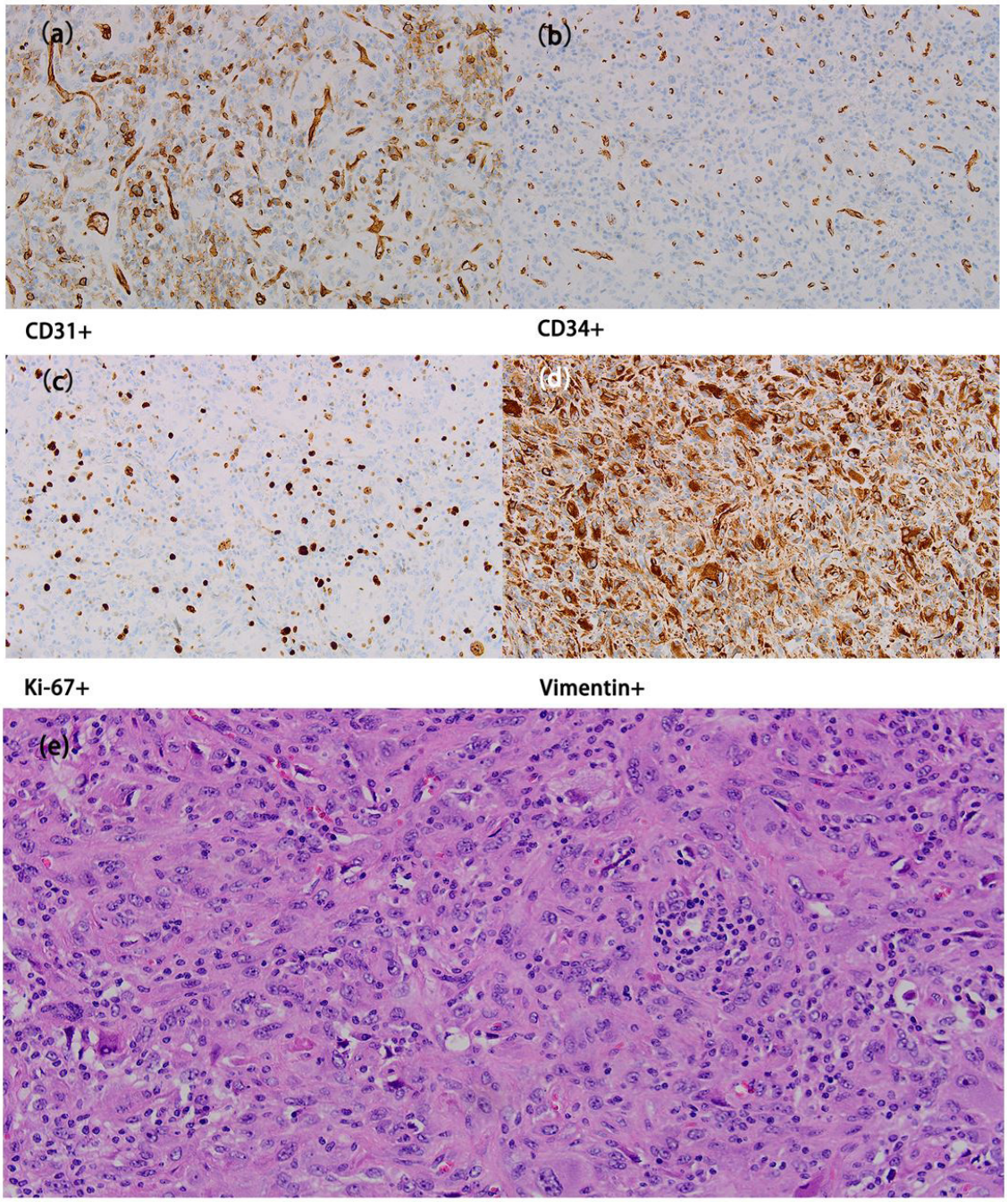


Figure 3: Pathological findings. Immunopositivity for (a) CD31, (b) CD34, (c) Ki-67 and (d) Vimentin (×200). (e) Markedly atypical cells which lack specific morphological features of differentiation was found by hematoxylin–eosin staining (H&E, ×200)

Discussion

PNP, first described by Anhalt et al. in 1990 [4], is a very rare but life-threatening immune system disease that is particularly prone to occur in patients with benign and malignant neoplasms. Clinically, PNP is most common in older patients aged 45 to 70 years and may also occur in younger patients [1]. As one of the main causes of death in PNP patients, the incidence of bronchiolitis obliterans is up to 30% [5]. Bronchiolitis obliterans can lead to respiratory failure with a fatal outcome.

The diagnosis of PNP is established based on clinical characteristics, concurrent internal neoplasia, histological examination, immunofluorescence, enzyme-like immunoassays and immunoprecipitation tests [5]. Nonetheless, this patient refused to undergo a skin biopsy. Enzyme-linked immunosorbent assay (ELISA) is also an effective measure for quantitative detection of circulating autoantibodies in PNP patients, showing quite high sensitivity and specificity [5]. A study showed that circulating anti-desmoglein 3 IgG can be detected in approximately 80% of PNP patients, and approximately 40% of patients found circulating autoantibodies against bullous pemphigoid antigen

180 (BP180) [5]. In addition, the presence of a neoplasm is often found in approximately 30% of cases prior to PNP. Clinically, the diagnosis of PNP is very tough due to atypical clinical manifestations. The differential diagnosis of PNP includes pemphigus vulgaris, erythema multiforme, and mucous membrane pemphigoid, etc. In this case, the patient was initially misdiagnosed with drug-induced stomatitis as a result of the use of cephalosporin. Generally, drug-induced mild erythema multiforme is common in erythema-papular type, which mainly accumulated on the extended side of the face, neck and distal extremities. After discontinuation of suspected sensitizing drugs, it can gradually disappear after symptomatic treatment. However, the patient only had oral mucosal ulcer erosion, which lasted for a long time, and it was still gradually aggravated after the withdrawal of cephalosporins. In addition, Pemphigus vulgaris also needs to be distinguished. The the degree of oral ulcer erosion of pemphigus vulgaris is mild, while skin damage area is large. Conversely, the patient initially presented with severe damage to the oral mucosa, but the degree of skin damage is less severe. Fortunately, anti-desmoglein 1 and anti-desmoglein 3 antibodies but not BP180 were detected by ELISA in the serum of this patient, which favor the the diagnosis of PNP.

Owing to the rarity of the disease, the treatment of PNP is still full of challenges. When PNP is suspected, Frew et al. proposed six treatment steps for a better prognosis, which included the stability of vital signs, evaluation for the underlying malignancy, clear diagnosis of PNP, feasible removal of trigger neoplasms, and therapy of PNP utilizing immunosuppression, immunomodulation, or plasmapheresis [6]. The mortality rate for PNP has been reported to be up to 90%, so the first step is crucial for patients [1,6].

Although high-dose corticosteroids can ameliorate only skin lesions but not stomatitis, they are still recommended as the first-line therapy for PNP [6]. In fact, the most important clinical feature of PNP is the resistance of mucosal lesions to most therapeutic strategies [6]. It has been reported that corticosteroids used in combination with other drugs (such as azathioprine, cyclosporine, mycophenolate mofetil, and intravenous immunoglobulin) have a good effect on PNP skin lesions [6]. However, mucosal lesions are also generally insensitive to these protocols [6]. Similarly, removal of triggered neoplasms had a certain inhibitory effect on the progression of PNP, possibly due to the reduced production of autoantibodies. Rituximab, an anti-CD20 monoclonal antibody, has shown good efficacy, especially in patients with PNP caused by B-cell lymphoma [7]. When first-line treatment fails, the association between rituximab and intravenous immunoglobulin can also be chosen [7]. Alemtuzumab, a CD52 monoclonal antibody against both B and T lymphocytes, has been reported by Hohwy et al. and has been successful in inducing both B lymphocyte chronic lymphocytic leukemia and PNP/PAMS (paraneoplastic autoimmune multiorgan syndrome) [8].

Conclusion

In conclusion, when patients with DDL or other malignancies develop pleomorphic skin lesions, such as cutaneous erythema, intractable oral erosion, or other mucosal lesions, the possibility of PNP should be considered. At the same time, laboratory findings should be performed as soon as possible. Due to the polymorphism of skin lesions, we should try our best to avoid misdiagnosis to save the lives of patients.

Conflict of interest

None declared.

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