Paraneoplastic Pemphigus with Underlying Retroperitoneal Inflammatory Myofibroblastic Tumor: A Case Report and Review of the Literature

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Abstract

Inflammatory myofibroblastic tumor (IMT) is a peculiar low-grade neoplasm of spindle cell fibroblasts and myofibroblasts in an inflammatory background. The lung is the most common site of involvement. Here, we report a case of paraneoplastic pemphigus (PNP)-associated with an extensive retroperitoneal IMT. The patient had a favourable response following treatment with a low dose of systemic steroid, mycophenolate mofetil, and intravenous immunoglobulin (IVIG). He subsequently underwent surgery for resection of the tumor with nephrectomy and five courses of IVIG were administered after surgery due to a minor relapse. He was in remission in her last follow-up visit 16 months after surgery. The occurrence of PNP with IMT is notable; early detection and treatment are crucial for this tumor-associated autoimmune disease.

Keywords: *Inflammatory myofibroblastic tumor, intravenous immunoglobulin, paraneoplastic pemphigus, retroperitoneum*

Introduction

Paraneoplastic pemphigus (PNP) is an immunobullous disorder in association with underlying neoplasms.[1,2] Inflammatory myofibroblastic tumor (IMT) is a peculiar low-grade sarcoma that is rarely associated with PNP especially retroperitoneal IMT.[3] In this paper, we describe a case of PNP associated with extensive retroperitoneal IMT and favourable response to intravenous immunoglobulin (IVIG).

Case Report

A 31-year-old man presented to our clinic with fever and painful mucocutaneous erosions. He had a history of oral lesions for 20 months. The patient was being treated with tenofovir for hepatitis B virus infection since 2 years ago. Physical examination revealed severe erosions of the oral mucosa, lips, conjunctiva, and genitalia together with generalized flaccid blisters, lichen planus-like, dusky and targetoid skin lesions. Paronychial and nail involvement was also observed [Figure 1a and b].

Histopathological examination of lesional specimen revealed focal suprabasilar acantholytic cleft, many apoptotic cells, basal layer damage, infiltration of dermal lymphocytes, and pigment incontinence. Direct immunofluorescence (DIF) evaluation of perilesional specimen showed intercellular suprabasal deposition of IgG and linear deposition of C3 along dermoepidermal junction. These findings were consistent with PNP [Figure 2a-c].

Due to a history of flank pain from one month ago and for evaluation of underlying malignancies, an abdomino-pelvic computed tomography scan (CT scan with contrast) was done. It revealed a large, hyper-enhanced, retroperitoneal mass (110 × 84 mm) with adherence to the left renal artery and vein. A CT-guided core needle biopsy showed a lesion composed of haphazardly arranged bland spindle cells with high vascularity and an intense inflammatory reaction rich in lymphocytes with a lesser number of plasma cells, eosinophils, and occasional mast cells [Figure 2d]. Immunohistochemistry study showed positivity of the spindle cells for SMA, Alk and Ki-67 (maximally 4–5%) and negative staining for LCA (only positive in infiltrated lymphocytes), CD34 (only positive in vascular walls), vimentin, desmin, CD99, CKAE1/AE3, and EMA. These findings were consistent with the diagnosis of an IMT. Chest CT scan and serum protein electrophoresis were normal. A surgery was done for tumor excision but

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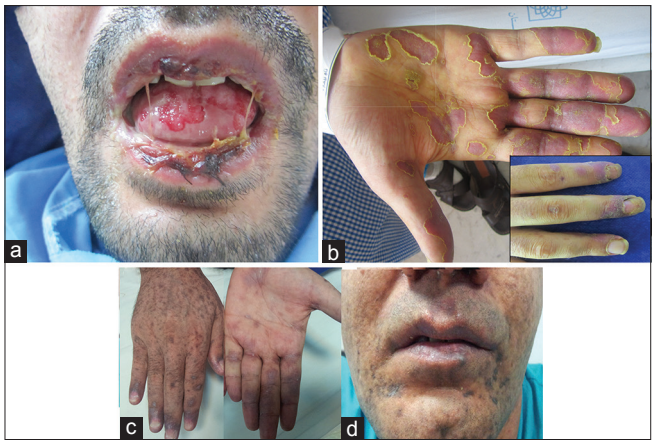

Figure 1: Clinical presentation. (a) At first admission, severe erosions of the vermilion border and the tongue (b) erosive lesions on the palm (inset: also paronychial and nail involvement). (c) After 8 months, skin erosions had disappeared along with lichenoid hyperpigmentation

it could not be removed due to its adhesion to vital vessels; chemotherapy was also not possible because of the poor general condition of the patient.

Clinical course

HBV.DNA viral load was <5 IU/ml. We started oral prednisolone (30 mg/day), mycophenolate mofetil (MMF) (2 g/day) and IVIG (400 mg/kg/day for 5 consecutive days). The erosive lesions became crusted after 7 days and the patient had partial improvement. IVIG was administered for 7 other cycles (every month). The patient showed a gradual clearance of the cutaneous lesions with post inflammatory lichenoid hyperpigmentation and satisfactory improvement of mucosal lesions [Figure 1c]. He subsequently underwent surgery for resection of the tumor with nephrectomy and five other courses of IVIG were administered due to a minor relapse, while the gradual tapering of prednisolone was continued and MMF discontinued. He was in remission on a minimum dose of prednisolone (10 mg/day) on his last follow-up visit (16 months after surgery).

Discussion

According to the revised criteria by Camisa and Helm, three major or two major and two minor signs are required for diagnosis of PNP. Major signs are polymorphous mucocutanous eruptions, coexisting internal neoplasia, and specific serum immunoprecipitation. Minor signs are histologic evidence of acantholysis, DIF findings of keratinocyte cell surface/basement membrane zone staining with IgG and C3, and indirect immunofluorescence staining of transitional epithelium (the rat bladder epithelium).[4]

Our patient had two major (the skin eruption and the neoplasm) and two minor (histology and DIF) signs, hence we confirmed this diagnosis.

PNP is a distinct immunobullous disorder in association with underlying neoplasms, either malignant or benign.

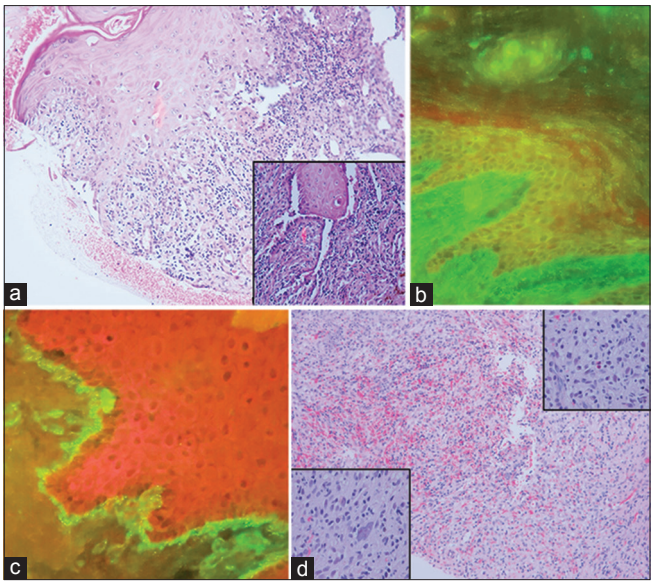

Figure 2: Histopathological evaluation of the mucocutaneous lesions (a-c) and retroperitoneal mass (d). (a) Many apoptotic cells, basal layer damage and infiltration of dermal lymphocytes; inset: also a suprabasilar cleft with acantholysis (H and E, ×200 and ×400). (b) Intercellular suprabasal deposition of IgG and (c) linear deposition of C3 along dermoepidermal junction (Direct immunofluorescence). (d) A lesion composed of bland spindle cells with high vascularity and dense inflammatory reaction rich in lymphocytes with a lesser number of plasma cells and eosinophils (see insets) (H and E, ×200 and ×400)

Sarcoma is an underlying malignancy in 6% of the cases of PNP.[1] IMT is a peculiar low-grade sarcoma that is rarely associated with PNP. The exact aetiology of IMT is unknown, but cytogenetic clonality have been detected and also an immune-autoimmune mechanism has been involved.[4,5] In general, IMTs are rare, including <1% of all surgically resected lung lesions.[3] The lung is the most common site. An uncommon site is the retroperitoneum. In a series of 84 cases with extrapulmonary IMTs, only 4 patients had retroperitoneal type.[5]

The appearance of PNP has been rarely reported in patients with IMT. One possible explanation could be a severe inflammatory response of the body to IMT.[3] The literature review showed five reported cases of PNP associated with IMT [Table 1].

In management of PNP, the majority of cases with benign tumors will ameliorate or clear completely after surgical resection; but there is no common consent on a standard effective treatment about malignant neoplasms. Complete resolution of the malignancy and a slow amelioration of the cutaneous lesions may occur after tumor-specific chemotherapy; although in general, the stomatitis is refractory to treatment modalities, our patient had a good response to treatment.[6] Various treatments with variable results have been used such as high-dose systemic steroids, azathioprine, MMF, IVIG, and rituximab.[7,8]

On the other hand, prediction of the biologic behaviour of IMT is difficult. The mainstay of the treatment is also

Table 1: Clinical findings in 6 patients with a confirmed diagnosis of paraneoplastic pemphigus and IMT

Author/Year	Sex/Age	Tumor site	Treatment	Bronchiolitis obliterans	Final outcome	Patient survival
Schoen/1998	M/16	Retroclavicular region	Immunoapheresis after tumor resection	No	Favourable	Patient's recovery
Mar/2003	F/11	Retroperitoneum	Tumor resection, prednisolone, methotrexate, gold	Yes	Progressive pulmonary involvement, died about 4 months after surgery	14 months
Kahawita/2006	F/23	Retroperitoneum	Dexamethasone, cyclophosphamide, no surgery owing to poor general condition	Yes	Progressive pulmonary involvement, died 4 days after the onset of hypoxia	3 months
Lee/2007	F/48	Costodiaphragmatic angle, originating from the 12th intercostal nerve	Tumor resection, prednisolone, cyclosporine, IVIG	Yes	Progressive pulmonary compromise, died 3 months after surgery	About 7 months
Ghandi/2015	F/30	Anterior mediastinum	Tumor resection, prednisolone, azathioprine, IVIG	No	Favourable	About 14 months (alive at the time of writing)
The presented case	M/31	Retroperitoneum	IVIG, MMF and low dose of oral steroid, after 8 months underwent surgery with nephrectomy	No	Favourable	24 months (alive at the time of writing)

F: Female, IMT: Inflammatory myofibroblastic tumor, M: Male

surgical excision. These tumors, especially retroperitoneal forms, may be unresectable due to their proximity to vital organs, as in our case; so recurrence may occur because of incomplete resections. Unfortunately, chemo (radio) therapy have no demonstrable benefit.[5] Our patient had hepatitis B virus infection; so the treatment choices were limited and using many immunosuppressants was not safe; however, we started him on a regular IVIG regimen every 4 weeks, oral MMF, and a low dose of systemic steroid. Fortunately, he showed a favourable response. Recently, IVIG has been used successfully in the treatment of many autoimmune blistering disorders. It is also an option in situations where other immunosuppressants are not safe (as in our patient).[8] Also, IVIG at the time of surgery may prevent the occurrence of bronchiolitis obliterans.[9] With the exception of our patient and also the case of Ghandi *et al.*,[3] fatal bronchiolitis obliterans occurred in all PNP cases associated with IMT [Table 1]. It has been shown that early diagnosis and using IVIG before and during surgical excision can reduce the mortality risk from bronchiolitis obliterans.[10]

In summary, PNP has high mortality owing to its resistant nature to treatment modalities and the disease course can be severe with development of bronchiolitis obliterans. Successful treatment has been reported only in a few cases. In our experience, IVIG is safe and effective in patients with PNP especially for reduction of the total dose of systemic steroids and avoidance of immunosuppression. Besides, it is important to note that patients with retroperitoneal IMT must be followed up even after surgery because of the possible late recurrence.[5]

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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