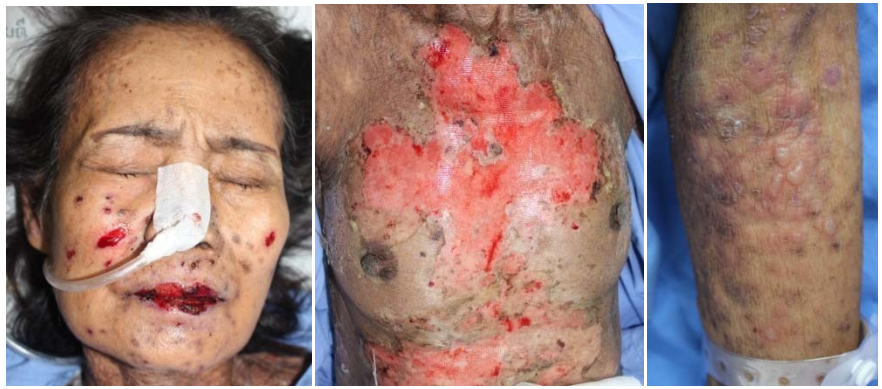
Case 2
A 71 year-old woman from Bangkok

Chief complaint: Severe mucocutaneous erosions for 2 months



(Fig. 2.1)

Present illness: The patient developed painful bilateral conjuntivitis, orogenital erosions, and multiple erosions on trunk for 2 months. She denied history of the new drug, photosensitivity, arthritis, prolong fever, and weight loss.

Past history: Her underlying diseases include diabetes mellitus, hypertension, and dyslipidemia.

Family history: No family history of malignancy

Physical examination:

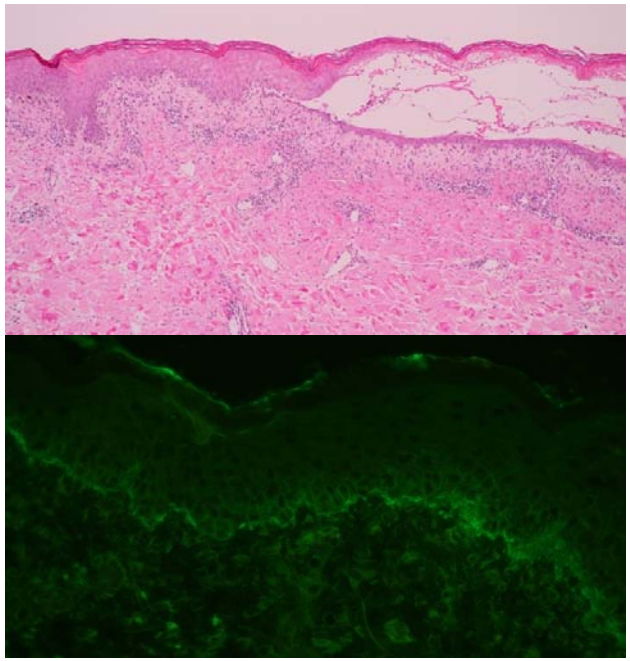
Dermatological examination: (Fig. 2.1) Multiple ill-defined dusky red to brownish macules coalescing into patches with erosions on trunk.

Mucosal examination: Multiple erosions on oral and genital mucosa. Bilateral conjunctival injection

Other systems: No lymphadenopathy, no hepatosplenomegaly

Investigation: Anti-Desmoglein (DsG) 3 Antibody > 200 U/mL (0-20 U/ML)

Histopathology: (S17-018182, Left thigh) (Fig. 2.2)



(Fig. 2.2)

Hematoxylin and eosin (H&E)

- Dense superficial perivascular and lichenoid infiltrate of lymphocytes, numerous eosinophils, and melanophages

- Suprabasal acantholytic blister and focal interface change with scattered necrotic keratinocytes at adjacent intact skin

Direct immunofluorescence (DIF): Intercellular deposition of IgG, C3, and linear deposits of IgG, C3 at dermoepidermal junction (DEJ)

Indirect immunofluorescence (IIF) from rat bladder epithelium: Negative

Computed tomography (CT) whole abdomen: Homogeneous infiltrative retroperitoneal lesion and fibrosis encircling along aorta, inferior vena cava and bilateral ureters, resulting in bilateral hydronephrosis

Diagnosis: Paraneoplastic pemphigus

Treatment: Intravenous dexamethasone 15 mg/day, then switched to oral prednisolone 20 mg/day

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Discussion:

Paraneoplastic pemphigus (PNP) is an autoimmune blistering condition that can affect multiple organs other than the skin. It is a life-threatening disease associated with an underlying malignancy.[1] Hematologic malignancy is the most common associated condition. These include non-Hodgkin's lymphoma (38.6%), chronic lymphocytic leukemia (18.4%), Castleman's disease (18.4%), thymoma (5.5%), Waldenstrom macroglobulinemia (1.2%), Hodgkin's lymphoma (0.6%), and monoclonal gammopathy (0.6%). Non-hematological neoplasms include carcinomas (8.6%), sarcomas (6.2%), melanoma (0.6%), and others (1.3%).[2]

Etiopathogenesis of PNP is not fully described. Skin lesions are thought to be originated by an antibody-mediated autoimmune response to tumor antigens that cross-react with epithelial antigens. Tumor autoantibodies produce and release cytokines (e.g., interleukin-6, etc.) that enhance B-cells differentiation and foster to develop the humoral response.[3] Some histopathological findings of individual keratinocyte necrosis with lymphocyte exocytosis support the role of cell-mediated immunity. The hypothesized that both humoral and cellular immune response were evoked by tumor antigens.[4] The presence of autoantibodies to plakins is a characteristic feature of PNP. Envoplakin and periplakin antibody levels are most specific, followed by desmoplakin I and II.

Various lesions may occur in patients with PNP. Typically, the first symptoms are painful intractable stomatitis, as well as the conjunctivae and anogenital regions.[5] The cutaneous lesions usually appear after the onset of mucosal lesions and may involve any site, mostly the upper part of the body. Cutaneous lesions can be classified into several groups according to the types of changes such as pemphigus-like, bullous pemphigoid-like, erythema multiforme-like, graft-versus-host-disease-like, and lichen planus-like.[6]

The disease often required several biopsies to achieve the diagnosis. Histology varies depending on the type of skin lesions such as epidermal acantholysis, suprabasal cleft formation, dyskeratotic keratinocytes, vacuolar changes in the basal epidermis, and epidermal exocytosis of inflammatory cells.[1]

DIF performed on a perilesional biopsy may reveal intercellular deposits of IgG and C3 autoantibodies, and linear deposits of IgG or C3 at DEJ. IIF from rat bladder epithelium reveals

intercellular IgG staining at transitional epithelium. The sensitivity and specificity of IIF technique for the diagnosis of PNP is 75% and 83%, respectively.[7]

Treatment of PNP is tumor excision, a surgical cure is often the best chance of inducing remission of PNP. First line medications are systemic corticosteroids (prednisolone 0.5-1 mg/kg/day) and rituximab.[8] Second line medications are *mycophenolate* mofetil, cyclosporin A, intravenous immunoglobulin (IVIG), cyclophosphamide, and plasmapheresis.

The overall prognosis of PNP is poor. The mortality rate ranges from 75% to 90%. The main cause of death is bronchiolitis obliterans, followed by sepsis.[9] The prognosis is better when the disease is associated with benign tumors and may even remit when tumors are excised.

References:

1. Tirado-Sánchez A, Bonifaz A. Paraneoplastic Pemphigus. A Life-Threatening Autoimmune Blistering Disease. Actas Dermosifiliogr 2017;8:30370-8.
2. Tirado-Sánchez A, Leon-Dorantes G. Paraneoplastic pemphigus associated with malignant fibrous histiocytoma. Int J Dermatol 2006;45:1374-5.
3. Anhalt GJ. Paraneoplastic pemphigus: the role of tumours and drugs. Br J Dermatol 2001;144:1102-4.
4. Zimmermann J, Bahmer F, Rose C, Zillikens D, Schmidt E. Clinical and immunopathological spectrum of paraneoplastic pemphigus. J Dtsch Dermatol Ges 2010;8:598-606.
5. Meyers SJ, Varley GA, Meisler DM, Camisa C, Wander AH. Conjunctival involvement in paraneoplastic pemphigus. Am J Ophthalmol 1992;114 :621-4.
6. Nguyen VT, Ndoye A, Bassler KD, Shultz LD, Shields MC, Ruben BS, et al. Classification, clinical manifestations, and immunopathological mechanisms of the epithelial variant of paraneoplastic autoimmune multiorgan syndrome: a reappraisal of paraneoplastic pemphigus. Arch Dermatol 2001;137:193-206.
7. Arbache ST, Nogueira TG, Delgado L, Miyamoto D, Aoki V. Immunofluorescence testing in the diagnosis of autoimmune blistering diseases: overview of 10-year experience. An Bras Dermatol 2014;89:885-9.
8. Sehgal VN, Srivastava G. Paraneoplastic pemphigus/paraneoplastic autoimmune multiorgan syndrome. Int J Dermatol 2009;48:162-4.
9. Bronnimann M, von Felbert V, Streit M, Hunziker T, Braathen LR. Progressive respiratory failure in paraneoplastic pemphigus associated with chronic lymphocytic leukemia. Dermatology 2004;208:251-4.