A severe vesicobullous eruption associated to esophageal carcinoma: case based review

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Summary
Paraneoplastic autoimmune multiorgan syndrome (PAMS) is a life-threatening autoimmune mucocutaneous disorder associated with underlying neoplasms, particularly hematologic or lymphoproliferative. Solid neoplasms associated with this condition have been less frequently reported. We report the case of a 65-year-old female with PAMS associated to an unresectable esophageal carcinoma.

KEY WORDS: PAMS; paraneoplastic; esophageal carcinoma.

Introduction
Paraneoplastic autoimmune multiorgan syndrome (PAMS), initially termed paraneoplastic pemphigus by Anhalt et al. (1), is an autoimmune disorder that typically targets mucocutaneous epithelia (2). Although the majority of PAMS cases have been associated to hematologic malignancies or lymphoproliferative diseases, solid neoplasms have also been occasionally reported (2). Most cases occur between 45 and 70 years of age and men are more frequently affected than women. A significant association of PAMS with HLA class II DRB*03 has been reported (3). PAMS frequently affects internal organs with predilection towards the bronchial epithelia resulting in bronchiolitis obliterans and rapid progression into an often fatal respiratory failure (2). This condition is commonly resistant to treatment, with an associated high mortality (90% mortality) (4). We present, to the best of our knowledge, the second case report of PAMS associated with esophageal squamous cell carcinoma (SCC).

Case report
A 65-year-old woman recently diagnosed with an unresectable esophageal SCC was consulted to our service with a nine-day history of a progressive mucocutaneous eruption involving the oral mucosae, trunk and extremities. Upon physical examination the patient presented multiple erosions in the buccal mucosa, tongue, soft palate, and severe hemorrhagic crusting of the lips (Figure 1a). The chest, trunk and upper extremities presented vesicles, flaccid bullae, target-like lesions and confluent areas of denudation (Figure 1b). The clinical differential diagnosis included Steven-Johnsons/toxic epidermal necrolysis overlap, pemphigus vulgaris and PAMS. Histopathological examination of a bulla on the chest showed an intraepidermal vesicle with acantholysis (Figure 1c). Direct immunofluorescence (DIF) revealed intercellular deposition of IgG (Figure 1d) and linear deposition of IgM (Figure 1e) along the basement membrane, fulfilling the diagnostic criteria for PAMS.

The patient was started in high-dose intravenous corticosteroid treatment (equivalent to 125 mg of prednisone daily). New lesions stopped appearing by four days of treatment and one week later the skin and mucosal lesions started to re-epithelialize. Corticosteroid dose was tapered down and the patient was discharged home two weeks later on 60 mg of prednisone daily with almost complete cutaneous and oral mucosa re-epithelialization.

The patient was scheduled to start chemotherapy for the esophageal carcinoma, but one week after discharge she started again with skin lesions and returned to the Emergency Room (ER). Upon examination, the patient presented again with erosions of the oral mucosa and lips, and vesicobullous lesions with confluent denudation in the trunk, extremities, inguinal area, and face (Figure 2). The lesions covered 60% of body surface area. A skin biopsy of an intact vesicle was performed, but the patient died of a cardiorespiratory arrest less than 24 hours after arrival to the ER. Posthumous histopathological examination demonstrated an intraepidermal blister with acantholysis. Family members refused an autopsy.
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Figure 1 - (a) oral mucosa showing diffuse erosions and hemorrhagic crusting of the lips; (b) multiple vesicles, bullae, and erosions in the upper extremity; (c) histopathology showing intraepidermal vesicle with suprabasilar acantholysis (Hematoxylin-eosin, 10x); (d) DIF showing deposition of immunoglobulin G in the epidermal intercellular spaces (DIF, 20x); (e) DIF showing deposition of immunoglobulin M in the basement membrane (DIF, 10x).

Figure 2 - TEN-like confluent denudation in the upper trunk.
Discussion

Patients with PAMS typically present with a painful, progressive and intractable stomatitis of the oral mucosa and lips, considered by some the hallmark of the disease and usually the initial clinical manifestation (5-7). Cutaneous involvement has been described as polymorphous, with individual patients presenting with different types of skin lesions: blisters, erosions, patches, papules and plaques. Clinical variants include pemphigus-like, bullous pemphigoid-like, erythema multiforme (or toxic epidermal necrolysis-like), graft-versus-host-disease-like, and lichen planus-like (7). Histopathological findings correlate with the specific clinical variant. The histopathologic hallmark is an interface vacuolar reaction pattern or an interface lichenoid reaction pattern. Intraepidermal blisters with acantholysis may also be present (7). Direct immunofluorescence findings of mucocutaneous lesions demonstrate three distinct staining patterns of autoantibody deposition: pemphigus-like intercellular staining, linear pemphigoid-like staining at the basement membrane zone, and homogeneous or apoptosis-like staining of the entire cell (7). Circulating autoantibodies have been detected by indirect immunofluorescence of mucocutaneous lesions suggestive of pemphigus vulgaris or TEN, but suspicion for PAMS when patients present with skin lesions suggestive of pemphigus vulgaris or TEN, but with associated severe and intractable erosions of the oral mucosa and lips. Diagnostic tests including skin biopsy, DIF, IIF, and immunoprecipitation/imunoblot studies should be promptly performed in order to establish the diagnosis. Once the diagnosis of PAMS is established, if not already present, a thorough search for an underlying malignancy is warranted with emphasis on lymphoproliferative disorders. If such malignancies are not found, a search for other less commonly reported malignancies must ensue. Patients like the one presented here with non-resectable tumors invariably have a dismal prognosis.

Most experts believe high-dose corticosteroid therapy (0.5-1 mg/kg) is the treatment of choice with or without concomitant immunosuppressive agents such as cyclosporine (5 mg/kg) and cyclophosphamide (2 mg/kg) (4). Other reports highlight alternative therapies such as immunoablative high-dose cyclophosphamide without stem cell rescue, immunopheresis, intravenous immunoglobulin, rituximab and alemtuzumab (14-18).

To the best of our knowledge, only one case of PAMS with esophageal SCC has been previously reported in the English language literature. Hyun Cho et al. (19) reported a 68-year-old male with PAMS and metastatic esophageal SCC with skin lesions that progressed rapidly despite treatment with chemotherapy and high-dose steroids. The patient eventually died of sepsis. Three case reports were considered by Hyun Cho et al. (19) to represent previously reported patients with paraneoplastic pemphigus and esophageal SCC. A patient with “pemphigus vulgaris” and esophageal SCC was reported by Takahashi et al. (20). The authors never considered the diagnosis of PAMS and never reported immunofluorescence or immunoprecipitation test results, failing to fulfill the diagnostic criteria for PAMS. The two other cases cited by Hyun Cho et al. (19) as representing cases of PAMS with esophageal SCC were written many years before the initial report of Anhalt et al. (1) in 1990 and were written in foreign languages (21, 22).

Our patient with PAMS displayed an unusual combination of features: a clinical presentation mimicking TEN, an infrequently reported presentation, and an underlying esophageal carcinoma, only the second such association reported in the literature. This case highlights the importance of maintaining a high index of suspicion for PAMS when patients present with skin lesions suggestive of pemphigus vulgaris or TEN, but with associated severe and intractable erosions of the oral mucosa and lips. Diagnostic tests including skin biopsy, DIF, IIF, and immunoprecipitation/imunoblot studies should be promptly performed in order to establish the diagnosis. Once the diagnosis of PAMS is established, if not already present, a thorough search for an underlying malignancy is warranted with emphasis on lymphoproliferative disorders. If such malignancies are not found, a search for other less commonly reported malignancies must ensue. Whenever possible, prompt resection of the tumor or, if unresectable, medical treatment directed at the underlying malignancy should be undertaken and initiation of systemic corticosteroids strongly considered. Patients and family members should be informed of the resistant, recalcitrant and highly mortal nature of this condition so that appropriate plans are made. Further research efforts are needed to unravel the pathogenesis of PAMS in order to find more directed...
and effective therapeutic regimens for this often fatal autoimmune condition. Because of its infrequent occurrence, multi-institutional cooperation will be required in order to recruit significant numbers of patients.

Disclosure
The Authors have no conflict of interest to disclose.

References