Clinical-pathologic conference: Cutaneous paraneoplastic pemphigus associated with benign encapsulated thymoma

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RADIOLOGY

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GYNECOLOGY

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Case Presentation

Dr Ortiz: The patient is a 62-year-old woman with a 90-pack-year smoking history who was seen with a chief complaint of intermittent skin lesions over her trunk and extremities for the past 3 years. The lesions had recently grown in size, and a large painful ulceration had appeared in her left groin. An extensive evaluation of the maculopapular skin lesions had been undertaken previously, and the working diagnosis of her dermatologist was Grover's disease.¹ During my evaluation a routine chest radiograph revealed an anterior mediastinal mass, which was verified by computed tomography to be a 7.5-cm circumscribed contrast-enhancing mass. On examination the patient appeared healthy, and her vital signs were within normal limits. Pertinent findings included distant breath sounds and a rash over her chest and extremities, which will be described in detail by Dr Boh. There was also an ulcerated lesion several centimeters in size in her left vulvar area, and this lesion will be addressed by Dr Lottinger. In anticipation of surgical removal of the patient's anterior mediastinal mass, pulmonary function tests were performed. Spirometry revealed a forced vital capacity that was 79% of predicted and a forced expiratory volume in 1 second that was 59% of predicted. Residual volume was 115%. The patient's electrocardiogram was abnormal, as were results of an exercise stress test. She therefore underwent cardiolyte stress testing with sestamibi, which demonstrated no ischemic changes; however, the mediastinal mass was evident, as will be discussed by Dr Campeau. The patient was then referred to Dr Hartz for surgical excision of the mass.

Dr Campeau: Computed chest tomography revealed a 7.5-cm circumscribed, contrast-enhancing mass with a central area of nonenhancement consistent with necrosis or cystic change. These findings were more evident on the nuclear myocardial stress test, which showed a large mediastinal mass with intense sestamibi activity but no central area devoid of activity (Figure 1).

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Dr Hartz: Dr Campeau, I was surprised to see such intense nuclear activity in an extracardiac location. Can you describe the significance of this finding?

Dr Campeau: Extracardiac sestamibi activity is occasionally evident on nuclear stress examinations. The finding is almost always significant, and the differential diagnosis of sestamibi activity in chest masses includes both benign and malignant processes. In this patient with an anterior mediastinal mass, the most probable diagnosis is thymoma, but despite the circumscribed appearance malignancy cannot be ruled out. Less likely possibilities include lymphoma and mediastinal teratoma.

Dr Ortiz: Dr Lottinger, can you describe the findings when the patient came to you for evaluation of the painful groin lesion?

Dr Lottinger: She had first noticed a blister in her left groin, which resolved spontaneously, 4 months previously. She then had a raised painful mass develop in a similar location a few months later. On examination, there was a 4 × 3-cm raised, weepy mass over the left labia majora and extending into the groin crease (Figure 2, A). There was no associated lymphadenopathy. A punch biopsy of the lesion 9 weeks before thymectomy revealed eosinophilic pustular dermatitis (Figure 2, B-D). Special stains for organisms, including fungi, were negative, and there were no granulomas seen. The differential diagnosis suggested by the dermatopathologist included pemphigus vegetans, blastomycosis, and halogenoderma. I offered complete excision of this painful mass, but the patient elected to defer this approach until after her chest surgery.

Dr Ortiz: Dr Boh, can you provide the rationale for the initial diagnosis of Grover's disease in this patient and also describe the results of the skin biopsies performed by you?

Dr Boh: Biopsy specimens of the crusted vesicular lesions on the patient's trunk initially demonstrated varying degrees of acantholysis and a lymphocytic or neutrophilic infiltrate with eosinophils. The acantholytic process and neutrophilic infiltrate were suggestive of Grover's disease, transient acantholytic dermatosis, or pemphigus, but the distribution of the lesions was atypical for Grover's disease. Because of the abnormal clinical and histologic patterns, our working diagnosis was transient acantholytic disease. Various therapies were used, but new lesions continued to develop.

Seven weeks after thymectomy, new pruritic vesicular pustules developed on the patient's left breast (Figure 3, A) and leg. Biopsy of the leg lesion demonstrated intraepidermal vesicular dermatitis with numerous eosinophils (Figure 3, b and c). Direct immunofluorescence done on the breast lesion showed granular and intercellular deposits of immunoglobulin (Ig) G, to a lesser degree for IgA and complement component C3, and faintly for IgM. There were also faint linear deposits of C3 at the dermoepidermal junction. These findings supported a diagnosis of pemphigus, and

Figure 1. Nuclear myocardial stress test. Note mass (thymic tumor) above left ventricular myocardium in left anterior oblique projection. Uptake of radioactivity is also noted beneath heart in liver.

possibly paraneoplastic pemphigus.² In view of the clinical presentation, I favored pemphigus erythematosus, an autoimmune vesicular eruption. The bullae are formed as a result of deposition of immunoreactants, primarily IgG and complement, in the intercellular spaces. Pemphigus erythematosus has been reported in patients with thymoma, both benign and malignant, with Castleman's disease, and with malignancies.

Dr Hartz: Although the radiographic evaluation suggested a benign thymic neoplasm, the paraneoplastic skin manifestations were worrisome. The patient was counseled about the potential malignant nature of the tumor and the fact that her pulmonary disease precluded sacrifice of a phrenic nerve (for complete removal) if the mass proved to be a malignant thymoma. She accepted these considerations and agreed to the operation. The mass was approached with a cosmetic, partial sternal-splitting incision. The sternotomy was J-shaped and extended into the left fourth intercostal space. Through this incision an extensive thymectomy was performed; this included skeletonization of the innominate vein and removal of all thymic tissue. There was a large encapsulated mass in the thymus, which will be described by Dr Daroca. The patient had no postoperative problems and was discharged home on day 3.

Dr Ortiz: Dr Hartz, can you explain the rationale for performing a limited sternotomy in this patient? Had this lesion been malignant in behavior, could all the tissue have been removed through this incision?

Dr Hartz: Recently cardiothoracic surgeons have become more adept at limited-access surgery, even for replacing heart valves and repairing intracardiac defects in infants. The operation performed on this patient is currently my

Figure 2. Left groin lesion. **A**, Gross photograph of ulcerated lesion before thymectomy. **B**, Photomicrograph demonstrating suprabasilar acantholytic dermatosis associated with epithelial hyperplasia and prominent dermal and intravesicular eosinophilia (hematoxylin and eosin, original magnification $\times 100$). **C**, Intraepidermal vesicle in stratum spinosum contains numerous eosinophils and devitalized acantholytic keratinocytes. This focus has features of intraepidermal eosinophilic abscess (hematoxylin and eosin, original magnification $\times 200$). **D**, In this $\times 400$ (original magnification) view, suprabasilar acantholytic vesicle contains neutrophils, eosinophils, and acantholytic keratinocyte.

preferred method of approaching anterior mediastinal masses. In this case, the patient's impaired pulmonary function was further impetus for this approach, because the body of the sternum was not separated from one side of the manubrium and she had no respiratory embarrassment after the operation. We have reported this approach in a series of patients, and it is diagramed in Figure 4. Dr Daroca, will you please describe the pathology of the tumor?

Dr Daroca: The resected thymic neoplasm is an encapsulated thymoma. The capsule is intact, and there is no evidence of invasion of mediastinal soft tissues accompanying the specimen. The tumor has prominent spindled cell patterns. There are also focal pseudorosettes, a well-described variant in thymoma. Small lymphocytes are dispersed throughout the background of the neoplasm. No areas of necrosis or cytologic atypia were noted. The pathologic findings are illustrated in Figure 5).

Dr Hartz: The patient was seen in follow up 6 weeks after surgery. At that time, the ulcerated lesion over her groin crease had resolved considerably and the macular skin lesions over her trunk were almost gone. The chest incision was well healed, and there was no seroma beneath the subcutaneous flap. The patient was contacted 2 years after surgery, at which time she stated that the groin lesion had completely resolved and not recurred. However, she had intermittent mild recurrences of the trunk and extremity lesions, which were being symptomatically controlled with dapsone. Dr Boh, what is the rationale for treating the skin lesions with this medication?

Dr Boh: Dapsone is often used as a steroid-sparing agent. This medication has a significant impact on lymphocyte and neutrophil chemostasis and also decreases pruritus. Because pemphigus erythematosus appears to involve activated lymphocytes and deposition of immunoreactants

Figure 3. Trunk lesions. **A**, Gross photograph of breast lesion. **B**, Histologic preparation of leg lesion shows vesical high in epidermis with few keratinocytes in roof of vesicle. Patterns in floor of vesicle are in keeping with re-epithelialization. Erythrocytes, occasional eosinophils, and granular proteinaceous material are present in vesicle. There is superficial perivascular dermal infiltrate of eosinophils and lymphocytes (hematoxylin and eosin, original magnification $\times 100$). **C**, In this section of leg lesion, dermis contains prominent perivascular eosinophilic infiltrate (hematoxylin and eosin, original magnification $\times 400$).

within the epidermis, dapsone and other immunomodulatory drugs appear to be effective therapy. Both pemphigus erythematosus and paraneoplastic pemphigus have been reported in the settings of thymoma and myasthenia gravis. In paraneoplastic pemphigus, patients have painful oral lesions in addition to acantholytic intraepidermal bullae.

Dr Hartz: Dr Daroca, can you explain the pathologic basis of the paraneoplastic manifestations in this patient?

Dr Daroca: Paraneoplastic pemphigus is a vesiculobullosus cutaneous disorder that is seen in association with internal neoplasms, especially those of lymphoid type. The initial criteria² outlined in 1990 for this cutaneous disorder

Figure 4. Diagrammatic representation of surgical incision. *Dotted line* represents skin incision. *Solid line* represents sternotomy.

included the following: (1) the development of mucosal erosions and a papular skin eruption that progresses to blistering and erosive lesions affecting the trunk, extremities, palms, and soles; (2) an occult or known neoplasm; (3) cutaneous histologic changes of interface dermatitis, keratinocytic necrosis, and intraepidermal acantholysis; (4) direct immunofluorescence showing deposits of IgG and C3 in the epidermal intercellular spaces and often granular or linear complement deposition along the epidermal basement membrane zone; and (5) serum antibodies that bind to cell surfaces of skin and mucosa in a pattern typical for pemphigus but also bind to transitional epithelium. Anhalt² observed that not all patients fulfill each of these criteria, that acantholysis is most readily detectable in the oral lesions of patients early in the course of the disease, and that the cutaneous lesions can be highly polymorphic. He also noted that blistering lesions may not occur in some patients but that treatment resistant stomatitis remains a constant feature of the disease. The cutaneous lesions are clinically polymorphic and may resemble an array of vesiculobullous disorders, including pemphigus vulgaris, erythema multiforme, pemphigus erythematosus, pemphigus vegetans, pemphigus foliaceus, cutaneous lupus erythematosus, bullous pemphigoid, cicatricial pemphigoid, and lichen planus pemphigoides. Patients with this disorder associated with a malignant neoplasm usually have a poor prognosis, although prolonged survival has been reported.²

Dr Hartz: Dr Daroca, I was somewhat confused by the fact that the biopsy specimens yielded different diagnoses.

Figure 5. Thymoma. **A**, In low-power photomicrograph, thymoma is surrounded by thick, fibrous capsule. Neoplastic thymic epithelial cells are suspended in lymphoid stroma (hematoxylin and eosin, original magnification $\times 100$). **B**, In this region, pseudorosettes of thymic epithelial cells are prominent (hematoxylin and eosin, original magnification $\times 200$). **C**, In another region, epithelial component of tumor is primarily spindled (hematoxylin and eosin, original magnification $\times 200$).

Is this typical for lesions of paraneoplastic pemphigus? Furthermore, this is the first case of paraneoplastic skin manifestations associated with a benign chest tumor that I

have personally treated. Can you elaborate on other conditions associated with paraneoplastic pemphigus?

Dr Daroca: As noted before, the histopathologic features are as variable as the polymorphous clinical cutaneous presentations, and indeed with this patient's biopsy specimens, categorization of her vesiculobullous cutaneous disease was somewhat problematic. The dermatopathologist included pemphigus vegetans in the differential diagnosis. Regarding your second question, neoplasms associated with paraneoplastic pemphigus include both benign and malignant neoplasms, the latter being more common, and are predominantly of hematopoietic or reticuloendothelial origin and include non-Hodgkin's and Hodgkin's lymphomas, chronic lymphocytic leukemia, lymphomatoid granulomatosis, mycosis fungoides, thymoma (benign and malignant), Castleman's disease, and Waldenström's macroglobulinemia. Other neoplasms associated with paraneoplastic pemphigus include Kaposi's sarcoma and carcinomas of the breast, skin, mucous membranes, lung, uterus and cervix, ovary, stomach, liver, and gastrointestinal tract.³

Cruz and associates⁴ described a patient with myasthenia gravis, a cutaneous disorder with features of pemphigus erythematosus or lupus erythematosus, and an encapsulated benign thymoma consisting of spindled cells. The skin eruption was present both before and after the removal of the thymoma. Oral and tongue ulcers were present. There was a clinical butterfly eruption, and histologic findings of an interface lichenoid dermatitis supported a diagnosis of cutaneous lupus erythematosus. Results of direct and indirect immunofluorescence studies were consistent with pemphigus erythematosus (intercellular substance antibody [IgG] in the mid and upper epidermis) and a focal granular (stippled) band of IgG and C3 at the dermoepidermal junction. In their review of the literature, Cruz and associates⁴ identified 16 cases of pemphigus associated with myasthenia gravis and thymoma, 11 associated with myasthenia gravis alone, and 8 associated with thymitis or thymoma alone. Almost half (43%) of the patients had pemphigus erythematosus, and another third had pemphigus vulgaris. The effect of thymic ablation on the course of the skin disease was variable. In a separate literature review, Younus and Ahmed³ noted that 18 cases of pemphigus and thymic neoplasia were reported. Pemphigus vulgaris and erythematosus were equally common in the setting of thymoma, each occurring in 44% of cases, and pemphigus foliaceus was seen in 11% of cases. Sixty-seven percent of patients had benign thymoma, and only 2 had malignant thymoma. The sequential relationship between the skin manifestations and thymoma was variable. In more than half of the cases the thymoma preceded pemphigus (mean 89 months), in 22% the thymoma was detected after the diagnosis of pemphigus (mean 25 months), and in only 1 case were the disorders diagnosed simultaneously. The association of

pemphigus, thymoma, and autoimmune disease was reviewed by Patten and Dijkstra.⁵ Myasthenia gravis is by far the most common associated autoimmune disease. Other autoimmune diseases include erythroid aplasia, systemic lupus erythematosus, and bullous pemphigoid. Pemphigus vulgaris, pemphigus erythematosus, and pemphigus foliaceus occur at nearly equal frequencies.

Dr Hartz: Dr Boh evaluated the patient for a connective tissue disorder, and the workup was negative. Is there an autoimmune background in this skin disorder?

Dr Daroca: Although the skin diseases in this setting are described under the rubric of paraneoplastic pemphigus, perhaps a more precise label would be cutaneous paraneoplastic autoimmune vesiculobullous disease. The autoantibodies in the serum of patients with paraneoplastic pemphigus immunoprecipitate a complex of high-molecular weight proteins from keratinocytes with relative molecular weights of 250, 230, 210, 190, and 170 kD. The 250-kD antigen is now known to represent desmoplakin I, and the 210-kD antigen represents desmoplakin II (desmosomal plaque proteins). The 230-kD antigen is bullous pemphigoid antigen.² Antibodies to a 130-kD antigen (similar to that seen in pemphigus vulgaris) have also been detected.⁶ The desmoplakins play a pivotal role in anchoring the network of intermediate filaments to desmosomes. The 130-kD antigen in pemphigus vulgaris is desmoglein 3. Desmogleins are desmosomal cadherins (calcium-dependent adhesion molecules). Desmoglein 3 is found primarily in the spinous layer of the epidermis and is the target antigen in pemphigus vulgaris. Desmoglein 1 is expressed primarily in the upper layer of the epidermis and is the target antigen in pemphigus foliaceus.⁶

Dr Hartz: Dr Daroca, after this extensive discussion, what is your final diagnosis of our patient's skin condition?

Dr Daroca: The histopathologic findings of the vesiculobullous cutaneous disorder in the present case share features with pemphigus vegetans. The biopsy specimen from the left groin best illustrates the active acantholytic process. Dr Boh will subsequently address clinical and direct immunofluorescent findings, which are not typical of pemphigus vegetans. The skin lesion represented in the leg biopsy specimen probably reflects an older, partially re-epithelialized nonacantholytic lesion. Pemphigus vegetans has been reported in the region of the vulva,⁷ and in pemphigus vegetans peripheral eosinophilia and oral lesions are frequent.⁸ Cases of pemphigus vegetans have been reported in association with the drugs captopril (an antihypertensive agent that is a competitive inhibitor of angiotensin I-converting enzyme) and with enalapril (a combination angiotensin-converting enzyme inhibitor and hydrochlorothiazide).^{9,10} Our patient was receiving neither of these medications. In the report by Bastiaens and colleagues,¹⁰ 1 of 3 patients with pemphigus vegetans had an associated

squamous cell carcinoma of the lung. The cutaneous lesions of pemphigus vegetans antedated the diagnosis of lung cancer by 3 months and were present in the left axilla and in both the right and left groins. The authors noted that the cutaneous lesions and circulating antibodies disappeared after removal of the tumor.

Dr Hartz: Dr Boh, are your diagnoses (pemphigus erythematosus and transient acantholytic dermatosis) consistent with Dr Daroca's impression of pemphigus vegetans?

Dr Boh: Pemphigus represents a spectrum of variants, including the classic pemphigus vulgaris, pemphigus erythematosus, and pemphigus vegetans. Clinically, pemphigus erythematosus has flaccid bullae and erosions, typically in a seborrheic distribution. Pemphigus vegetans has a heaped up lichenified or vegetative appearance, often without evidence of blisters or erosions. Although the groin lesion was acanthotic or thickened, the other clinical lesions were flaccid bullae and erosions without a thickened or vegetative appearance. The clinical appearance and distribution of the lesions, coupled with histologic and immunohistochemical studies, support the diagnosis of pemphigus erythematosus. Immunohistochemical analysis of a pemphigus vegetans lesion would show intercellular IgG but no linear band of immunoreactants at the dermal-epidermal junction. As you recall, there was a faint linear band of IgG at the dermal-epidermal junction in the breast biopsy specimen.

Dr Daroca: Perhaps the best label to describe this patient's cutaneous disorder would be paraneoplastic autoimmune vesiculobullous disease.

Dr Hartz: In summary, our patient had a benign thymoma and an associated paraneoplastic vesiculobullous

skin disorder that had variable clinical presentations and pathologic findings, depending both on the area of presentation (leg, breast, groin) and the duration of the eruption. A new variant of a partial sternotomy was used to remove the tumor. The patient did well after the operation, and the skin lesions were almost resolved within a few weeks. In patients with vesiculobullous skin lesions, a high index of suspicion is necessary to detect and treat associated neoplasms in a timely fashion.

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