Clinico-Pathologic Conference: Case 6

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Clinical Presentation

A 57-year-old Caucasian female was referred to the Dermatology clinic with a chief complaint of persistent unilateral palpebral edema. Prior to her visit, she had been empirically treated with antibiotics for a week, with no significant improvement. She did not complain of any discomfort, although she reported a ten-year history of non-specific muscle weakness. She did not report any fever, pain, weight loss, respiratory distress, or diaphoresis.

Her medical history included type-1 diabetes mellitus, bilateral carpal tunnel syndrome (surgically treated 2 years earlier), hypertension, hypothyroidism, and a pelvic fracture. Her prescribed medications were insulin, clonidine, aspirin, levothyroxine and folic acid. She did not smoke or use recreational drugs and her alcohol consumption was sporadic. She was allergic to penicillin, sulfa drugs, ramipril, captopril, levofloxacin, azithromycin, and was later found to have additional drug allergies.

The patient initially presented with periorbital edema only (Fig. 1). In the subsequent weeks, she developed

hemifacial edema combined with erythematous and violaceous plaques, some of which were also noted on the scalp (Fig. 2). Discrete areas of hyperpigmentation and fine telangiectasias were present in some of the involved areas. There were no other sites of skin involvement. Neurologic and intraoral examinations were within normal limits. Eventually, submandibular lymph nodes became palpable and slightly enlarged.

The initial biopsy revealed epidermal atrophy with focal interface dermatitis and keratotic plugging (Fig. 3). The dermis displayed stromal edema and increased mucin deposition, the latter of which was highlighted with an Alcian blue stain (Fig. 4). Perifolliculitis and deep perivascularitis composed almost exclusively of plasma cells and lymphocytes were noted (Fig. 5). Secondary melanin incontinence was also observed.

Differential Diagnosis

The most significant features of the patient's history, clinical, and histologic presentation are:

- periorbital edema/heliotrope rash
- poikilodermatous features
- submandibular lymphadenopathy
- carpal tunnel syndrome
- interface dermatitis, perivascularitis, and mucin deposition.

The consideration of the etiology of each of these is useful in the development of an appropriate differential diagnosis.

Periorbital edema has numerous causes including hypothyroidism and drug allergies, which the patient was known to exhibit. Infections, scleredema, nephrotic

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Fig. 1 Periorbital edema

syndrome secondary to diabetes mellitus, and cutaneous lupus erythematosus also may result in periorbital edema. By contrast, a heliotrope rash is pathognomonic of dermatomyositis.

Poikiloderma is defined as a combination of hyperpigmentation, telangiectasias and atrophy. Poikiloderma-like features are seen in numerous cutaneous diseases including lupus, dermatomyositis, cutaneous T-cell lymphomas and radiodermatitis.

Fig. 2 Erythematous/violaceous rash

Fig. 3 Keratotic plugging and perifolliculitis (H + E stain)

Fig. 4 Stromal edema and increased mucin deposition (H + E stain)

Fig. 5 Perivasculitis (H + E stain)

Submandibular lymphadenopathy is most often indicative of bacterial or viral infections of the scalp, paranasal sinuses, ears, eyes, neck, pharynx or oral cavity. The latter of these anatomical regions may be excluded for this patient based on the history. Other causes include lupus erythematosus, sarcoidosis, dermatomyositis, lymphoma, or metastatic disease.

Carpal tunnel syndrome (CTS) is associated with medical conditions including diabetes mellitus, myxedema, dermatomyositis [1] and deep morphea. Vocational activities are commonly associated with CTS. In this patient's case, since the history of CTS did not coincide with the onset of the skin lesions, the former was not considered to be a major feature in the elucidation of our diagnosis. However, a combined pathogenesis, or at the very least an underlying auto-immune susceptibility, could not be ruled out clinically.

The histologic appearance of the skin biopsy from our patient is most consistent with a diagnosis of lupus erythematosus but may also be observed in several conditions [2]. For instance, interface dermatitis is exhibited in lichenoid lesions, secondary syphilis, and anti-thyroid antibody associated interface dermatitis. Mucin deposition may also be seen in dermatomyositis, myxedema, scleroderma, and scleromyxedema. Perivascular dermatitis may occur in any condition causing erythema as well as in dermatomyositis and secondary syphilis.

In an attempt to organize this complex information, we sought a common denominator of all the aforementioned significant features. The patient may have a condition in which there is an overlap of lupus erythematosus, dermatomyositis and, to a lesser extent, scleroderma. This would be consistent with a diagnosis of mixed connective tissue disease. Paraneoplastic dermatomyositis is a final consideration if the submandibular lymphadenopathy is a result of a primary or metastatic malignancy preceding dermatomyositis.

Diagnosis and Discussion

The histopathologic features of the cutaneous biopsy are consistent with a diagnosis of discoid lupus erythematosus (DLE). However, early on in our investigation, this was viewed with increasing scepticism as several conflicting clinical features emerged. Indeed, DLE usually consists of well-demarcated erythematous plaques with scaling and eventual crusting, whereas the lesions in our case showed little scaling and were ill-defined and rather violaceous. Secondly, the typical onset of DLE is between the ages of 20 and 40 years, although late-onset DLE is possible. Furthermore, DLE often is associated with photosensitivity and usually responds well to therapy, both features being

absent in our case. In fact, our patient did not respond favorably to topical and systemic medication, which included antimalarial drugs and prednisone. Finally, the striking periorbital heliotrope rash is uncommon in DLE. It should be mentioned that DLE per se may coexist with a number of overlapping diseases including dermatomyositis, and has also been regarded as a paraneoplastic phenomenon in some case reports.

In view of the foregoing atypical features in our patient, the diagnosis of DLE was revised and replaced with dermatomyositis, possibly secondary to an underlying malignancy. At that point, a systematic investigation for an occult primary was undertaken. A computed tomography scan of the head and neck revealed multiple bilateral cervical lymph nodes, some of which displayed a convincing heterogeneous pattern (Fig. 6). The scan was otherwise unremarkable, although the interpretation was suboptimal since no intravenous contrast medium was used.

A needle-core biopsy of a suspicious cervical lymph node revealed nests of malignant squamous cells consistent with a diagnosis of metastatic squamous cell carcinoma. Complete examination, random biopsies and a tonsillectomy failed to identify a primary site.

The patient was treated by intensity-modulated radiotherapy with a total dose of 7000 cGy. The cutaneous lesions disappeared during the treatment, including the ones beyond the field of radiation, thus supporting a diagnosis of a paraneoplastic phenomenon. The patient is currently without disease, 3 years after treatment.

DM is an autoimmune disease that can be a part of polymyositis. It can affect any age-group and has a female predilection. Cutaneous manifestations of dermatomyositis

Fig. 6 Right heterogeneous cervical lymphadenopathy (arrows)

commonly include a heliotrope rash, Gottron's papules and poikilodermatous features. Muscle involvement may precede or follow skin involvement, and may actually never be present. Such a condition is termed dermatomyositis-sine myositis, also known as amyopathic dermatomyositis, and is characterized by typical cutaneous disease, no muscle weakness, and normal serum muscle enzyme levels for at least 2 years.

Histologic features of DM are quite variable, and may overlap with those of lupus, lichenoid drug eruptions and other immune-mediated conditions. Hence, clinical correlation is of utmost importance.

Malignancy is possible in any patient with dermatomyositis but is more common in patients after the age of 60 years. Paraneoplastic dermatomyositis has been reported with an extensive list of malignancies, including lymphomas, leukemias and carcinomas from the breast, lung, thyroid, bladder and other sites. In fact, a significant proportion of patients with DM have cancer.

The combination of DM and carcinoma of the head and neck has been widely reported [3]. In fact, DM appears to be one of the most common cutaneous paraneoplastic conditions associated with head and neck carcinoma. These conditions include paraneoplastic pemphigus, erythema multiforme, acanthosis nigricans, scleroderma, Sweet's syndrome and Leser-Trélat sign.

The exact pathogenesis of paraneoplastic DM is poorly understood and may involve several unidentified autoimmune mechanisms. In a correspondence by Nakamura et al. [4], interleukin-6-producing squamous cell carcinoma of the neck was thought to be a possible cause of a patient's DM. Kissel et al. [5] have suggested a complement-mediated pathway in DM-related vasculopathy. These findings

were corroborated by other studies [6] that have demonstrated an increased perivascular and junctional deposition of membrane attack complex (C5b-9) in lesional skin biopsies of DM patients. Magro and Crowson [7] have shown that the vascular deposition of C5b-9, as shown by immunofluorescence, may be an important tool in differentiating DM from lupus.

This case stressed the importance of considering a paraneoplastic phenomenon when dealing with DM, or with lesions exhibiting a lupus-like histology that do not respond to conventional therapy.

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