Clinical–Pathological Conference: Case 3

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Clinical Presentation

A 35 year old male, Brazilian, paper mill worker immigrated to the United States in 2006 and soon thereafter had an onset of nodules developing in areas he reported were bitten by mosquitos (Fig. 1). The nodules continued to enlarge and became diffuse. He sought help from the internet and a Brazilian “doctor” prescribed prednisone, 60 mg daily, which he took sporadically for about 1.5 years. He was also instructed to perform phlebotomy and inject the blood into his muscles. He did this himself with syringes obtained from a “doctor” at an internet site. When the condition worsened he was brought in 2007, by friends, to the clinic for evaluation.

The physical examination revealed diffuse infiltration of the skin, nasal mucosa and soft palate by thick papules and plaques some of which exhibited crusting and ulceration (Figs. 2, 3). There were no palpable cervical and upper and lower extremity nerves. There was no gross sensory or motor change of the hands and feet. The superficial lymph nodes and spleen were not palpable. Scleral injection was seen bilaterally.

Concurrent health problems included a *Strongyloides* infection successfully treated with Ivermectin in December 2008, and a conjunctival lymphangioma treated by excision in March 2009. The patient’s last visit was December 2009 at which time there was noted continued improvement with no new sensory or motor changes.

Differential Diagnosis

The hard and soft palates demonstrate thick, irregular, pink to slightly red papules and plaques situated along the midline. Small telangiectasias are present on the mucosal surface of the soft palate. The hard palate swelling shows focal ulceration. The upper and lower lips display multifocal nodular enlargement, without a change in skin or mucosal color.

The central, midline location, as opposed to a lateral site, along with involvement of both the hard and soft palate, suggests that this is not one of the relatively common entities that involve this region; namely, salivary gland neoplasms or squamous cell carcinoma. The location and appearance of the lesions are most consistent with a granulomatous infectious etiology. This is a broad category that may include fungal, bacterial, protozoal, or helminthic organisms. Deep fungal infections of consideration include histoplasmosis, blastomycosis, paracoccidioidomycosis, or cryptococcosis. Leprosy (Hansen disease) and tuberculosis are bacterial infections that should be contemplated, as should the protozoal infection leishmaniasis. Strongyloidiasis, a nematode infection, is also plausible due to the patient’s past medical history. Clinical manifestations of all of these diseases have been reported in this location, and with these infectious entities being contemplated, an underlying immunodeficiency should be ruled out.

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Fig. 1 Diffuse enlarging cutaneous nodules and plaques

Fig. 2 Skin and oral lesions consisting of papules and plaques with crusting and ulceration

Fig. 3 Nodular oral lesions with ulceration

Granulomatous mucositis due to non-infectious etiologies must also be included in the differential diagnosis. Orofacial granulomatosis may present with swelling of the lips in addition to mucosal hyperplasia of the palate. Foreign body reaction may have a similar clinical and histologic presentation. In addition, sarcoidosis can occasionally present circumorally within the lips and palate.

Other non-granulomatous disease, such as lymphoma and metastasis, must also be included in a thorough differential diagnosis. Non-Hodgkin's lymphoma can occur as extranodal disease within the oral cavity. It usually appears as a boggy, non-tender swelling of the palate, buccal mucosa, or gingiva, with or without ulceration. This diagnostic consideration is supported by the telangiectatic vessels seen on the patient's palatal mucosal surface, a feature that is often noted in mucosa overlying a malignancy. In addition, non-Hodgkin's lymphoma is further supported by the patient's professional history as a paper mill worker. This occupation is associated with numerous secondary malignancies due to the presence of multiple different carcinogens. Malignancies linked with a paper mill occupation include non-Hodgkin's and Hodgkin's lymphoma, nasopharyngeal carcinoma, mesothelioma, and other malignancies of the kidney, brain, esophagus, and gallbladder.

Diagnosis and Discussion

The histopathologic findings of a skin biopsy showed numerous foamy histiocytes without epithelioid granuloma formation (Fig. 4). Mycobacterial organisms were seen within histiocytes with Fite stain (Fig. 5). The clinical and histopathological findings were consistent with multibacillary leprosy.

Fig. 4 Sheets of foamy histiocytes in the dermis. H and E stain

Fig. 5 Acid-fast bacilli observed with Fite stain

A 2 year Multidrug therapy (MDT) was begun in June 2007 consisting of rifampin 300 mg daily, ofloxacin 400 mg daily, and minocycline 100 mg daily. Additionally, the patient takes 10 mg of prednisone daily and uses steroid eye drops 4 times per day. Dapsone was discontinued because of low levels of glucose 6 phosphate dehydrogenase. Due to the severity of his disease, as indicated by a bacterial index greater than 6, triple therapy will be continued with once monthly administration of rifampin, ofloxacin and minocycline. Follow-up visits have shown a steady decrease in the size of the mucocutaneous plaques and nodules.

Leprosy, caused by *Mycobacterium leprae*, is a slowly progressive highly infective disease with low pathogenicity and virulence [1]. Adults are relatively non-susceptible with conjugal leprosy affecting only 5% of those at risk [2]. Children, however, acquire the disease at a rate of 60% when one parent has leprosy [2]. It is probable that most infections in endemic areas begin in childhood but the long incubation period delays the expression of the disease. The incubation is typically 2–5 years but may be as long as 10–15 years. With the implementation of MDT, the number of active cases has dropped from 10 to 12 million in the 1980's to less than 2 million presently [1, 3]. The disease is predominantly seen in the tropics and sub-tropics, especially India and Brazil [1, 3]. The exact mechanism of transmission is not completely understood but is speculated that droplet infection may play a role because of the large number of organisms found in nasal secretions [2–5]. When infection occurs the cooler parts of the body are preferentially affected, most notably the skin, superficial peripheral nerves, nasal cavity and palate [1–4].

The manifestations of the disease depend upon the cell-mediated immune response an individual mounts against the organism. The variable immune response explains the vast range of clinical manifestations. Unlike tuberculosis, HIV has not had a significant impact on the worldwide

incidence of leprosy [1]. The World Health Organization (WHO), as reported by Moschella [1], defines a case of leprosy, in an untreated individual, as a person having one or more of the following 3 cardinal signs: (1) hypopigmented or erythematous skin lesions with loss of sensation, (2) thickening of peripheral nerves and (3) loss of sensation, or skin smear positive for acid-fast bacilli. Ridley and Jopling [6] classified leprosy into a 5 group system based on the immunologic response of the host. The most robust response results in tuberculoid leprosy and the weakest in lepromatous leprosy. The mid point of resistance is classified as borderline leprosy with borderline lepromatous and borderline tuberculoid intermediate. These intermediate types are less stable than the polar extremes and more likely to undergo change, typically moving towards the lepromatous pole.

Because in most endemic areas facilities for skin smears or biopsies are not available and the risk of utilizing poor techniques for smears increase the risk of transmission of diseases such as AIDS, the WHO decided to use a lesion count to determine multibacillary or paucibacillary disease for treatment purposes. Those patients with less than 5 skin lesions are paucibacillary and those with 5 or more lesions are multibacillary [7]. Diagnosis depends on clinical and histopathologic correlation [1, 4]. The specificity of skin smears are 100% however, only 50% or less of those infected will be positive [1]. Likewise, a biopsy may be non-diagnostic or equivocal, especially in the indeterminate type. A correlation between the Ridley–Jopling classification system and the WHO guidelines, used for clinical diagnosis, is as follows: (1) paucibacillary disease is equivalent to indeterminate leprosy, tuberculoid leprosy and borderline tuberculoid and (2) the multibacillary form is equivalent to borderline, borderline lepromatous and lepromatous leprosy.

The clinical expression of the disease depends on where the patient is found in the variable spectrum of the disease from tuberculoid to lepromatous. Nerves close by or in the area of the lesions are usually enlarged and tender. In multibacillary disease the lesions are more numerous and more symmetrically distributed. The lesions may be plaques which can be arcuate (especially in borderline cases) and less likely to be anesthetic. The neural involvement tends to be more symmetrical and involve the larger nerves in cooler parts of the body and the onset is slower and more insidious. Lepromatous leprosy can have diffuse infiltration of the skin, and in extreme cases, patients can exhibit a leonine facies when fibrosis creates deep lines in the forehead (Fig. 6), [2, 3].

Borderline tuberculoid disease clinically displays hypopigmented or annular plaque type lesions which are anesthetic. In borderline lepromatous disease the lesions can be annular and mixed with nodules and any associated

Fig. 6 Diffuse infiltration of the skin with fibrosis

neuropathy tends to be more symmetrically distributed than that seen in tuberculoid leprosy.

The neuropathy of leprosy is superficial sensory, motor and autonomic. The anterior chamber of the eye may be involved because of its relatively cool temperature.

Paucibacillary disease tends to have fewer lesions that are symmetrically distributed, flat or slightly raised and arcuate, erythematous or hypopigmented. The lesions can be scaly and anesthetic with palpable nerves especially in borderline cases.

Leprosy is not only an infectious process but, because of the body's immunologic response to the antigenic nature of the organism, it may stimulate a hypersensitivity response termed a reversal reaction. Reversal reactions are more common in patients with tuberculoid and borderline disease.

Lepromatous leprosy can involve the bone of the floor of the septum and bridge of the nose causing collapse of the midface resulting in the *facies leprosa* deformity. Bone loss in the anterior maxilla can result in tooth loss [2, 3, 5, 6].

Oral lesions are seen in 19–60% of patients and are almost exclusively found in the multibacillary form of the disease [2, 4, 7]. Yellow to red firm enlarging papules with ulceration and necrosis are most commonly seen on the hard and soft palate, labial gingiva, tongue, lips and buccal mucosa [3, 5, 8]. Lip involvement may result in notable enlargement easily confused with cheilitis granulomatosa. Facial paralysis and sensory deficits are possible.

The histopathologic findings are variably dependent on the type of leprosy present. Paucibacillary or tuberculoid leprosy produces well formed granulomas composed of epithelioid histiocytes and multi-nucleated giant cells. Any organisms present will only be visible when processed with an acid-fast stain such as the Fite stain. Lepromatous leprosy does not produce well formed granulomas but responds by forming sheets of vacuolated histiocytes mixed with lymphocytes. In the multibacillary form of the disease, numerous organisms will be found using an acid-fast stain [3, 4].

Multi-drug therapy varies for paucibacillary and multibacillary disease. Paucibacillary leprosy is treated with 600 mg rifampicin monthly supervised and 100 mg dapsone daily, unsupervised, for 6 months. For multibacillary leprosy 600 mg rifampicin and 300 mg clofazimine monthly, supervised, and 100 mg dapsone and 50 mg clofazimine daily for 12 months [9]. Following 6 months of treatment, the patient is considered non-infectious; however, because of the bactericidal effect of rifampin, the patient is likely non-infective after initiation of therapy [8]. Other anti-mycobacterial drugs that may be used if substitution is necessary are rifabutin, ofloxacin, sparflaxacin, levofloxacin, minocycline and clarithromycin [1]. Follow-up is recommended every 6 months for 5 years for paucibacillary leprosy and 10 years for multibacillary leprosy [9].

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