Laryngeal involvement with fatal outcome in progressive nodular histiocytosis: A rare case report

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ABSTRACT

Progressive nodular histiocytosis (PNH) represents a very rare type of non-Langerhans cell histiocytosis. It is characterized by progressive appearance of papules and nodules without spontaneous resolution. We report a 60-year-old patient with novel clinical features in the form of extensive noduloulcerative lesions, ichthyotic patches, and laryngeal involvement culminating in fatal outcome prior to therapeutic intervention. Although the presenting features were baffling, histopathology and immunohistochemistry clinched the diagnosis of PNH.

Key words: Laryngeal involvement, nodules, non-Langerhans cell histiocytosis

INTRODUCTION

Progressive nodular histiocytosis (PNH) belongs to an exceedingly rare family of non-neoplastic proliferative skin disorders known as non-Langerhans cell histiocytosis (NLCH).[1] First described by Taunton *et al*. in 1978,[2] it is one of the several variants, such as xanthoma disseminatum, generalized eruptive histiocytosis, multicentric reticulohistiocytosis and so on. In the past, there has been a great deal of confusion in classifying the various histiocytoses owing to rarity with which they were encountered as well as the tremendous overlap, both clinically and histologically, observed between these diseases.[1] Clinical, histopathological, and immunohistochemical correlation is required for differentiating PNH from other histiocytic disorders.

CASE REPORT

A 60-year-old man presented with asymptomatic reddish raised cutaneous lesions and significant weight loss since two years. Lesions gradually increased in size and number. He was initiated on multidrug therapy for leprosy with progressive worsening.

Physical examination showed multiple erythematous non-tender infiltrated papules and variably sized nodules over abdomen, back, neck, extremities, face, axillary, and inguinal areas.

Nodules over posterior axillary fold and trunk showed ulceration and verrucous margins [Figure 1]. Right eyelid involvement led to disfigurement and closure of palpebral fissure [Figure 2]. Laryngeal mucosa showed swelling, congestion, and cobblestoning on indirect laryngoscopy. Oropharyngeal, nasal and conjunctival mucosa were spared. Functional deformity of right leg was attributable to large lesion over right knee and ankle [Figure 3]. A few ichthyotic patches were noted on extremities [Figure 3]. There was no evidence of peripheral cutaneous nerve thickening or areas of sensory impairment. Systemic examination was unremarkable.

A clinical differential diagnosis of lepromatous leprosy, cutaneous T-cell lymphoma, diffuse

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cutaneous leishmaniasis, and histiocytosis was considered. Routine hematological and radiological investigations were normal. Histopathological examination of the nodule revealed ulcerated epidermis with dermal aggregates of proliferating spindle cells admixed with foamy macrophages [Figure 4]. Biopsy from ichthyotic patch demonstrated epidermal spongiosis and superficial perivascular infiltrates. There was no evidence of acid fast bacilli (on slit skin smear and on biopsy), abnormal lymphocytes, or intracellular amastigote forms (on Giemsa stain). A strong positivity for CD68 [Figure 5] and negative reaction for CD1a and S100 protein on immunohistochemistry, pointed to NLCH. Correlation of nodular lesions, progressive course, and histopathological and immunohistochemistry findings clinched diagnosis of PNH.

As part of screening, indirect laryngoscopy was performed which showed swelling, congestion, and cobblestoning due to infiltrated lesions over laryngeal mucosa with freely mobile vocal cords. As the patient was asymptomatic with patent airways, no active intervention was advised with regular clinical and laryngoscopic follow up. However, within a week of diagnosis, the patient suddenly became dyspneic and developed respiratory compromise probably due to obliteration of airways. Unfortunately, he succumbed prior to therapeutic intervention.

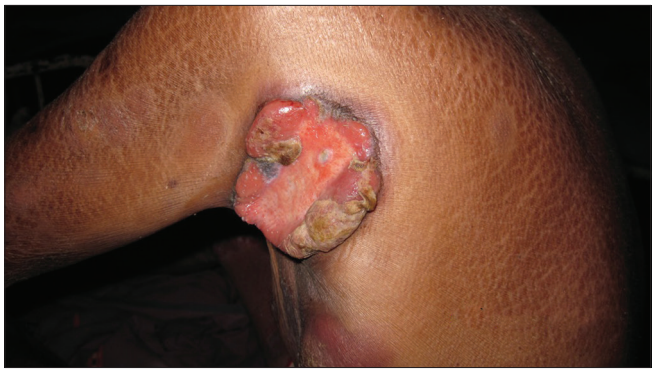

Figure 1: Large nodule with ulceration and crust over left side of posterior axillary fold region

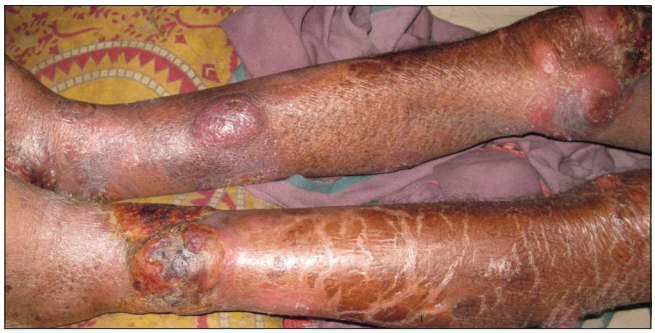

Figure 3: Large nodules over knees joint and ankle region with ulceration and crusting; note icthyotic patches over extensor aspect of legs

DISCUSSION

PNH is a rare variant of NLCH affecting skin and mucous membrane.[3] Defined by accumulation of histiocytes that do not meet the phenotypic criteria for diagnosis of LCH, they comprise a long list of diverse disorders, which have been difficult to categorize.[4,5]

There are two subgroups of NLCH. Class IIa (includes PNH)[6] involving dermal dendritic cells and Class IIb involving cells other than Langerhans cells and dermal dendrocytes. As is reflected in the name, most of the lesions in PNH (particularly well-established cases of long duration like ours) are nodules. Skin lesions are widely and randomly distributed on different body sites. Our patient showed characteristic large disfiguring facial nodules. However, unlike hitherto reported cases, he had large nodules over joint flexures

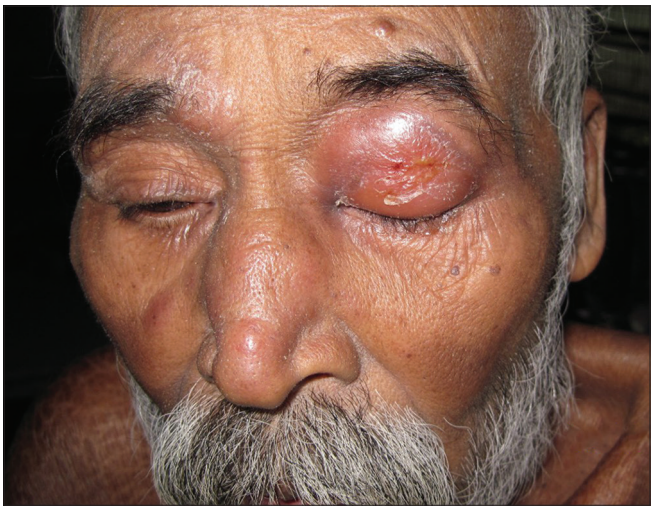

Figure 2: Infiltrated nodules over left eyelid, root of nose, and right eyebrow leading to facial disfigurement

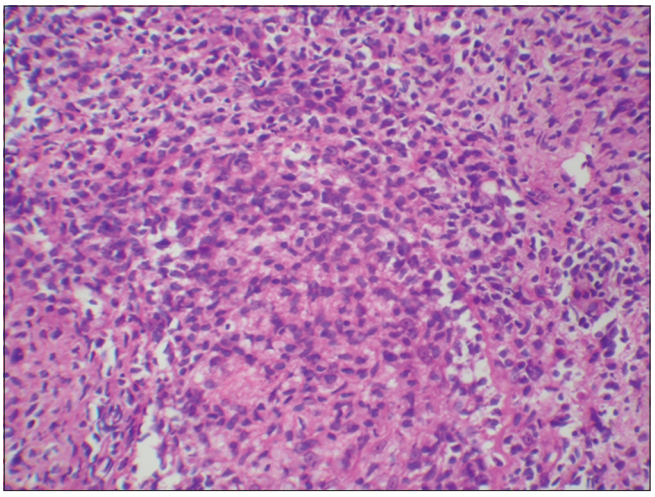

Figure 4: Dermis composed of spindle cells and foamy histiocytes (H and E, ×40)

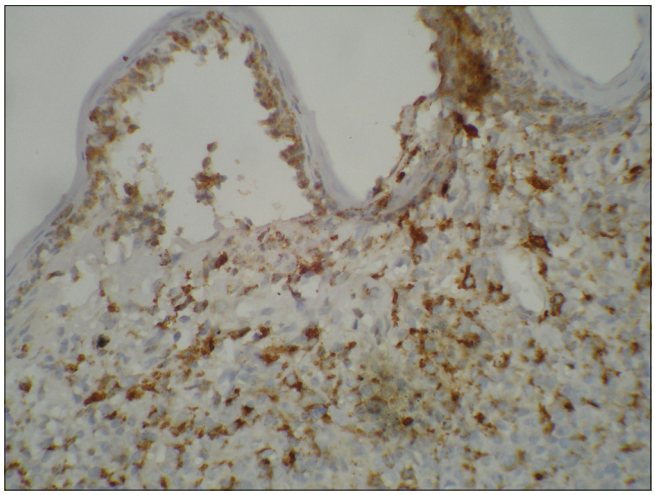

Figure 5: Immunohistochemistry -CD68 positive

causing impaired gait. PNH is regarded as a solely cutaneous disease without a tendency for extracutaneous involvement. In general, PNH is not known to be associated with specific systemic disorders or syndromes,[7] hence systemic screening may be indicated only in the presence of symptoms. Mucosal involvement, primarily seen in xanthoma disseminatum, can occur in any form.[8] Laryngeal affection encountered in our patient is considered an unusual feature. Indirect laryngoscopy showed nodularity and telangiectasia over vocal cords. It led to sudden respiratory difficulty culminating in death before any intervention. Mucosal involvement has been occasionally reported, including the publication by Taunton and colleagues who were the first to describe a patient of PNH with conjunctival lesions.[8] Karimi *et al*. and Glavin *et al*. claim to have documented the first case with extensive laryngeal and pharyngeal involvement causing dyspnea and dysphagia due to partial airway obstruction.[1,7] Hence after extensive search in the literature, only one previous case of PNH with laryngeal involvement could be identified (to the best of our knowledge). The presence of histiocytic infiltrates features in all forms of histiocytoses and is characterized by spindle-shaped, vacuolated, stellate, and foamy cells, all of which express immunohistochemical macrophage markers such as CD68.[8]

Criteria required for diagnosis of PNH include progressive course, presence of two different types of lesions, histopathology showing histiocytes and spindle cells in storiform pattern, and immunohistochemistry demonstrating CD68 positivity and CD1a and S100 negativity with absence of Birbeck granules on electron microscopy. Our patient satisfied the first four criteria (first two criteria are essential for diagnosis).[9]

Histopathological features and Ziehl–Neelsen (ZN) stain findings ruled out lepromatous leprosy, cutaneous T-cell lymphoma, and leishmaniasis. Finally, immunohistochemistry provided the vital clue to diagnosis of PNH. Treatment of PNH is usually unsatisfactory. Treatment modalities such as cyclophosphamide,[10] vincristine,[11] prednisolone,[11] azathioprine,[12] 6-mercaptopurine[12], Psoralen plus UVA,[13] have been tried by previous authors without much improvement. Reddy *et al*. reported successful use of methotrexate in a single case of PNH with cutaneous lesions.[12] Nakayashiki *et al*. performed effective surgical excision of cutaneous nodules without recurrence.[14] Williams *et al*. recently described the use of Imatinib and Pazopanib (in a patient having PNH with Eale's disease), which had to be discontinued due to lack of response.[15]

Our patient had unusual features, which deserve attention. He presented with nodules as the predominant lesion with few papules, which might suggest evolved or more mature progressive form of disease. The presence of infiltrated nodules with ichthyotic patches was misleading and further delayed the correct diagnosis. Ichthyotic patches have been hitherto unreported in PNH. It was unclear from the history offered by the patient as to whether these lesions preceded or followed initiation of multidrug therapy for Hansen's disease. In case of the latter situation, they were probably induced by clofazimine. Involvement of laryngeal mucosa by large nodules precipitated catastrophic respiratory compromise and unfortunately the patient succumbed before institution of any specific therapeutic measures.

In conclusion, rare disorders such as NLCH can mimic leprosy and hence must be considered in the differential diagnosis of patients presenting with infiltrated lesions. A high index of suspicion can facilitate early diagnosis and improve outcomes. Special attention to upper aerodigestive system is critical to detect rare but potentially life-threatening airway lesions. Despite its generally benign nature, our case illustrates the possibility (albeit remote) of poor outcomes in patients with mucosal (specifically laryngeal) involvement and underlines the importance of timely and aggressive management.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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