Neurofibroma Presented as an Additional Pathologic Finding in a Non-Nerofibromatosis Patient with Bullous Pemphigoid: A Case Report

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Abstract--- Background: Bullous pemphigoid (BP) is the most common autoimmune subepidermal blistering disorder, histopathologically composed of subepidermal split with a superficial perivascular inflammatory infiltrate, numerous eosinophils and intersperesed mast cells. On the other hand neurofibroma (NF) is a benign soft tissue tumor, which is composed of Schwann cells,fibroblasts, perineurial cells, endothelial cells, lymphocytes and mast cells.
Case Presentation: We present a case of 65-years-old woman without history of Neurofibromatosis presented with hemorrhagic tense bullae, erosions and erythematous lesions on her trunk which histopathologic examination of her skin lesion biopsy revealed coincidence of NF and BP.
Conclusion: To best of our knowledge the coincidence of NF and BP is a rare combination histologically, especially in a non-neurofibromatosis patient. The mutual presence of mast cells in both lesions could lighten the path for future investigations.

Keywords--- Dermatology, Histopathlogy, Dermatopathology, Bullous Pemphigoid, Neurofibroma, Neurofibromatosis Type 1, Mast Cell.

I. Introduction

Bullous pemphigoid (BP) is the most common autoimmune subepidermal blistering disorder, representing 80% of subepidermal immunobullous cases. [1] Bullous pemphigoid most commonly affects elderly patients between the ages of 60 to 80 years. [2] While the clinical presentation of bullous pemphigoid is broad, the immunobullous skin disorder characteristically presents with tense bullae and intense generalized pruritus. In atypical cases, bullous lesions may be absent, and these cases require a high degree of clinical suspicion. [3] Histopathology will reveal a subepidermal split with a superficial perivascular inflammatory infiltrate and numerous eosinophils. Spongiosis and superficial papillary dermal infiltrate of eosinophils without vesiculation are characteristic features of urticarial lesions and may indicate the dermatopathologist to a diagnosis of urticarial or pre-bullous pemphigoid. [4] In these cases, direct immunofluorescence studies are imperative. Direct immunofluorescence involves directly detecting tissue bound autoantibodies and is the gold standard of evaluation in autoimmune blistering diseases. It is imperative to biopsy the site of the skin lesion to get direct immunofluorescence. At least 2 punch biopsies should be obtained at the time of evaluation: one to send for hematoxylin and eosin staining, and the other is perilesional, uninvolved skin for direct immunofluorescence. DIF pattern for bullous pemphigoid will show deposition of C3 and IgG in a linear homogeneous pattern at the basement membrane zone. [5] In the early stages of this skin disease, only C3 may be present.[6] A salt-split skin immunofluorescence study may be done where the patient serum is applied on the salt-split skin, which splits the skin at the level of the lamina lucida. Bullous pemphigoid immunoreactants will localize to the epidermal side of the preparation, versus epidermolysis bullosa acquisita, which localizes to the dermal side. [7][8] ELISA testing to detect antibodies to the NC16A domain of BP180, also known as BPAG2, is available and has a sensitivity of 89% and specificity of 98%. Autoantibodies to BP180 and BP230 may be identified in normal subjects without bullous pemphigoid, but they will not bind to the NC16A domain. [9][10] Treatment depends on the severity of the disease; however, standard therapies involve topical or systemic immunosuppressive agents.[11] Prognosis varies, and long-term monitoring is often required.

Neurofibromas are the most prevalent benign peripheral nerve sheath tumor affecting men and women equally, without racial or ethnic predilection [12], often appearing as a soft, skin-colored papule or small subcutaneous nodule. They arise from endoneurium and the connective tissues of peripheral nerve sheaths. [13] Macroscopically often an unencapsulated, well-circumscribed, grey-tan firm mass. Typically ovoid or fusiform, with a pale

gelatinous cut surface. Usually, no areas of degeneration, necrosis, or hemorrhage are grossly identified. There may be transected nerve fibers attached to the mass forming portion of the lesion. [14] The plexiform type is often large, with multiple tortuous nerve fascicles, grossly described as a "bag of worms". Microscopically NFs are low to moderately cellular and composed ofloose and haphazard spindled cells withpoorly defined cell borders in background of myxoid to pale pink collagenous matrix. Coarse collagen bundles are present and often described as "shredded carrots".Mast cells commonly found within the lesion.Rarely, may encounter multinucleated giant cells, absent to minimal mitoses and may also occur within the nerve (intraneural localized neurofibroma) [14][15] Immunohistochemical Evaluation reveals : S100 (+) in Schwann cells (approximately 50% of tumor cells), CD34 (+) in spindled fibroblasts with distinct "fingerprint" immunopositivity (The "fingerprint" is due to positive staining between whorled collagen bundles, resembling a human fingerprint - this "fingerprint," if present in greater than 60% of the lesion, is useful in diagnosing neurofibroma and distinguishing neurofibroma from early desmoplastic melanoma), EMA (+) in occasional perineural cells, Myelin basic protein (+), Neurofilament protein (+) in intratumoral axons and Acid mucopolysaccharides (+) in mucinous stroma [15][16][17] Approximately 90% of cases occur sporadically, while the remaining cases are associated with neurofibromatosis type 1 or 2. [18][19] In both sporadic and syndromic cases, neurofibromas are a result of a deletion in the NF1 gene. In sporadic cases, only the lesional cells carry the NF1 mutation. In syndromic cases, neurofibromas are the result of a germline mutation in NF1, encoding the tumor suppressor protein neurofibromin, on chromosome 17q11.2. [20][21] Although the majority of neurofibromas occur sporadically and have an extremely low risk of malignant transformation, the plexiform type is pathognomonic for neurofibromatosis type 1 (NF 1). It carries an increased risk of malignant transformation. [22] The complete excision of the lesion is curative. [23]

In a case report by Shiomi T., the author reports two cases of Bullous pemphigoid (BP) with neurofibroma (NF)-like histopathological change. The two patients without neurofibromatosis type 1 (NF1) presented with several bullae on their trunk. Based on the results of positivity for anti-BP180 antibody, direct immunofluorescence, and histopathological findings, they were diagnosed with BP. Histologically, another lesion in the dermis, which was composed of spindle cells with wavy nuclei, collagen fibers, and mast cells, was located close to the bulla. Immunohistochemically, the spindle cells were diffusely positive for S-100 protein and CD34, and weakly positive for epithelial membrane antigen in certain foci. These findings were considered to be "NF-like" histopathological change. This is the first two cases of BP with NF-like histopathological change in patients without NF1. [24]

II. Case Report

The patient was a 65 years old diabetic woman without history of Neurofibromatosis (gene analysis was not performed) presented with generalized several hemorrahgic bullae, erosions, and erythematous lesions on her trunk and limbs since 2 months ago. (Fig1) As she described, primarily the lesions were pruritic wheel- like erythemas on her abdomen (prodromal lesion). She has only been taking medications for the diabetes management prior to the skin condition. Physical examination of oral mucosa shows no involvement (pure cutaneous) and no other clinically significant findings were identified through the use of observation, palpation, percussion, and auscultation integrated with the patient's history.

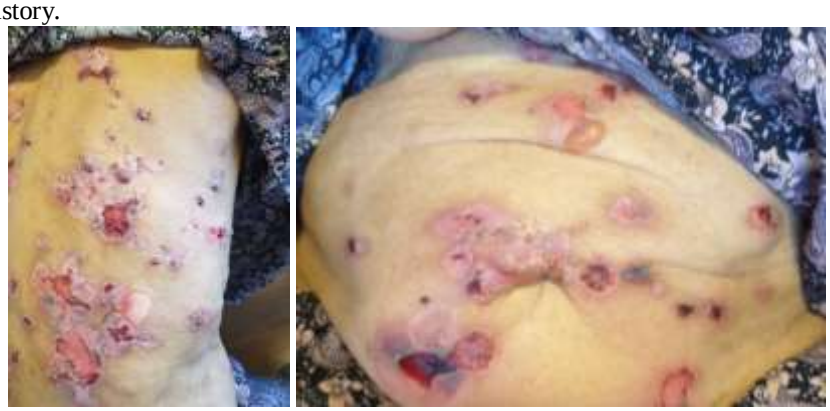

Fig. 1a,b: Clinical Picture, Several Hemorrahgic Bullae, Erosions and Erythematous Lesions on her Trunk (Posterior, Anterior)

With three main differential diagnosis in mind which were Pemphigus Vulgaris (PV), Bullous Pemphigoid (BP) and Dermatitis Herpetiformis (DH) biopsy from one of the abdominal bulla was taken by dermatologist and sent for histopathological evaluation.

Histopathological findings include a subepidermal bulla that was infiltrated withmixed inflammatory cells including many eosinophils, lymphocytes. Eosinophils infiltrations include superficial perivascular areas, in the

papillary dermis, blister cavity and lined up along the dermal epidermal junction and extended into the epidermis (eosinophilic spongiosis).(Fig2a,b)

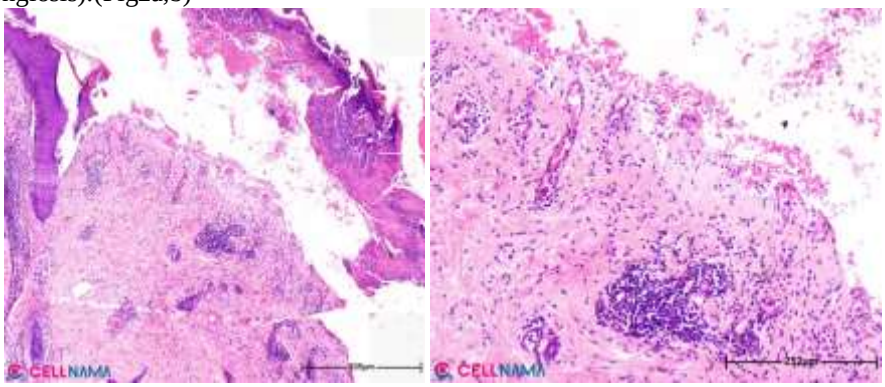

Fig. 2a,b: There is a Subepidermal Bulla Beneath which there is a Mixed Cell Infiltrate including Eosinophils & lymphocytes (H&E, x100, x200)

These findings were consistent with Eosinophil rich Bullous pemphigoid which was well appreciated by direct immunofluorescence (DIF) showing intense linear basement membrane zone staining for IgG &C3. (Fig 3).

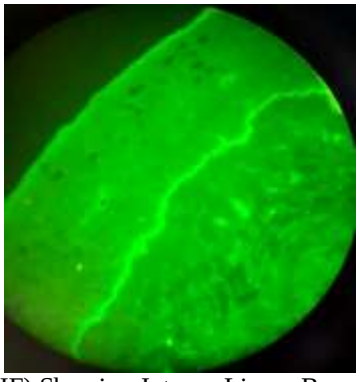

Fig. 3: Direct Immunofluorescence (DIF) Showing Intense Linear Basement Membrane Zone Staining for IgG

Additionally, underneath the subepidermal blister a well circumscribed but not encapsulated lesion was phenomenally evident in the dermis, which was composed of spindle cells withwavy serpentine nuclei and pointed ends, interspersed shredded carrot like collagen fibersand mast cells. The latter findings were typically diagnostic of Neurofibroma, therefore no additional evaluation were needed for confirmation. (Fig. 4a,b,c).

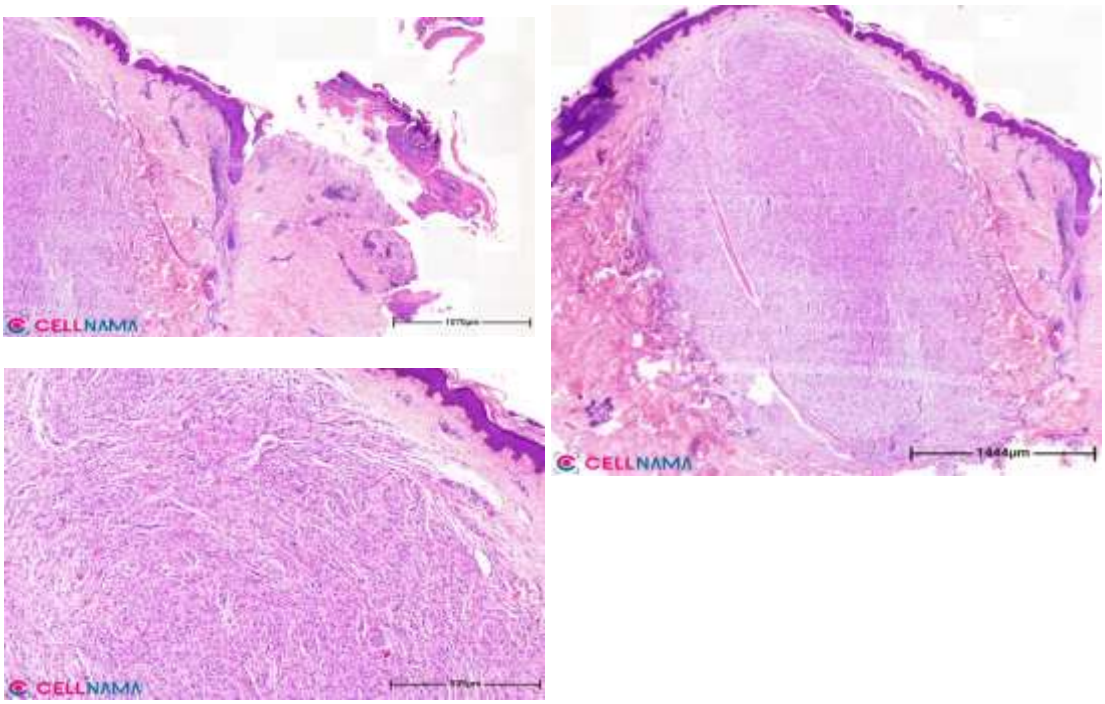

Fig. 4 a,b,c: Underneath the Subepidermalblister there is a Well Circumscribed but not Encapsulated Dermal Lesion, which was Composed of Spindle Cells with Wavy Serpentine Nuclei, Interspersed Shredded Carrot like Collagen Fibers and Mast Cells. (H&E, x100, x100 ,x200)

III. Discussion

The patient had no clinically identifiable nodules around the bullae. The skin lesions improved with oral administrationof prednisolone in a month, which is considered a standard treatment for BP. NF, was appropriate for the additional dermal histological findings in the patient. Other peripheral neuronal lesions, such as schwannoma were considered in the differential diagnosis of the patient. However, absense of Verocay bodies, nuclear palisading and hyalinized thickening of vessel walls ruled out the diagnosis.

Autoantibodies against BP180 and/or BP230 play a major role in pathogenesis of BP. [25] The binding of autoantibodies to the sehemidesmosome structural proteins causes inflammatory responses including complement activation and mast cells degranulation.Subsequently, activated eosinophils and neutrophils release different proteolytic enzymes. The inflammatory process injures tissue with adisruption of dermoepidermal adhesion, resulting in subepidermal blisters. [25] Regarding NF, it is a benign soft tissue tumor, which is composed of Schwann cells, fibroblasts, perineurial cells,endothelial cells, lymphocytes, and mast cells. [26] Mast cells are usually prominent in NF and canbe helpful to diagnose histologically. Most cases of NF present with solitary, localised, cutaneous lesions. The etiology and pathogenesis of solitary NF are not well known. [27] Meanwhile, multiple NFs are the cardinal feature of NF1. NF1 results from inherited or de novo germline mutations in the NF1 tumor suppressor gene that encodes the protein neurofibromin and normally down-regulates RAS signaling. [28] The microenvironment of NF1, especially infiltration of mast cells induced by chemoattractant stem cell factors or local trauma, contributes to formation of NFs. [26] In the presence of themutation, secretion of various cytokines from mast cells causes proliferation of Schwann cells, fibroblasts, perineurial cells, and endothelialcells, leading to NF formation. [29] Thus, mast cells are a common important factor in both BP and NF. Yesudian et al.[30] reporteda case of BP accompanied by NFs in a patient with NF1 and considered that mast cells might play akey role in the genesis. Interestingly, infiltration of mast cells was observed in the current case. Mast cells are basically derived from the bonemarrow and are released into the blood. Afterleaving the vasculature, these mature cells are normally located in the endoneurial, perineurial,and epineurial spaces of peripheral nerves. [31] Nerve damage induces increased accumulation of mast cells.[31] Although the possibility that both BP and NF coexisted incidentally could not be excluded, mast cells induced by BP causing tissue injury could have been anessential histogenetic factor in NF.

IV. Conclusion

To the best of our knowledge, this is the second report of BP accompanied by NF/ NF-like histopathological change in patients without NF1 regarding Shiomi T. case repot. [24] We speculate the histopathological change

could be related with BP in the current case. However, only one biopsy could be evaluated in our patient followed for a limited term. On the other hand the mutual presence of mast cells in both lesions could be a lead in order to clarify the exact genesis and clinicopathological significance of this coincidence in future investigations.

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