

Sebaceous induction: a common observation in neurofibroma regardless of the anatomical sites

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ABSTRACT

Background: Neurofibroma (NFs) has multiple histopathological variants. The tumors themselves are composed of Schwann cells, fibroblasts, mast cells, and perineural cells with a mixture of collagen and extracellular matrix.

Objective: To assess how frequent is sebaceous induction in neurofibroma and if it can be considered as a clue for diagnosis.

Methods: 100 cases of NFs were retrospectively collected, reviewed and assessed for sebaceous induction. All slides were pulled from the archive of the pathology department at King Hussein Medical Center from 2012 until 2016 with use of the key word 'neurofibromas'. Moreover, other histopathological features of NFs and any associated epidermal changes were also evaluated.

Results: Sebaceous induction was present in 22% of all NFs, the sites of distribution for NFs with sebaceous induction are as follows :Upper extremities (3%), lower extremities (1%), chest (4%), back (5%), abdomen (3%), neck (4%), perianal (1%), ear lobe (1%), scalp (5%), no follicular induction was noticed.

Conclusion: Sebaceous induction is an interesting and not uncommonly observed feature in NFs, occurring on different locations in a high percentage of the cases studied. Sebaceous induction in NFs is not site-specific. However, further studies with larger sample size is needed to further elaborate the significance of this finding.

Keywords: Sebaceous induction, Neurofibroma, Follicular induction, Spindle cell.

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Introduction

Neurofibroma may occur as a solitary tumor or as multiple lesions which may assume a wide distribution or segmental in pattern. All NFs types are histologically and clinically identical in behavior whether they occur as a part of neurofibromatosis or as solitary tumors distinct from neurofibromatosis. [1]

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Cutaneous neurofibroma presents itself as a mass that protrudes just above the surface of the skin or lies under the skin with an overlying violaceous hue. They are softer than the surrounding connective tissue, often creating a “buttonholing” sensation when a finger is rubbed gently over the surface. Neurofibromas show no site of predilection, although they rarely occur on the palms and soles. They can develop anywhere on the skin, and there is a wide variation in their shape and size. They are considered as one of the hallmarks of neurofibromatosis. [2, 3]

Microscopically, NFs consists of spindle cells (Schwann cells, fibroblasts, and perineural cells) with thin elongated wavy nuclei that regularly spaced between collagen bundles in a loose matrix. The spacing between adnexal structures is usually preserved. [4] Mast cells as a histopathologic clue are sparse between spindle cells. Mitoses in classic examples of NFs are uncommon, but mitotic figures can be frequent in atypical variants or those that develop in the context of neurofibromatosis. [1] Several histopathological variants have been described including extraneural, sporadic cutaneous NF (ENSCN), diffuse NF, intraneural NF, and plexiform NF.[4] The histologic differential diagnoses for NF include a number of neoplastic and non-neoplastic neuronal lesions such as schwannoma, nerve sheath myxoma, ganglioneuroma, traumatic neuroma and non-neuronal neoplasms such as dermatofibrosarcoma protuberance.

The term “sebaceous induction” should be precisely defined. Ackerman et al. described sebaceous induction as “a single lobule, unaffiliated with a hair follicle or several lobules joined in a normal fashion to a villous follicle by a sebaceous duct. [5] In another study, sebaceous induction was defined as more than one rudimentary sebaceous glands overlying the lesion at an abnormally superficial level of the dermis without a normal hair follicle associated with them. [6].

Follicular induction is defined as the formation of germ (nubbins of basaloid cells on the undersurface of the epidermis) and associated papillae or formation of rudimentary villous hair and associated sebaceous gland in a very superficial location.

Although the histopathologic diagnosis of NFs in most cases is straightforward, sometimes is challenging when other possible diagnoses such as dermatofibrosarcoma protuberance (DFSP) or other spindle cell neoplasms come into the consideration, specifically when the pathologist is dealing with superficial biopsies. In this study, we assessed the frequency of sebaceous induction in NF and whether or not it can be used as a histopathologic clue for diagnosis of it.

Materials and methods

This is a retrospective study of 100 cases of neurofibromas. All slides were pulled from the archive of the pathology department at King Hussein Medical Center from 2012 until 2016 with use of the key word 'neurofibromas'. A senior dermatologist and a dermatopathologist reviewed all cases for following

parameters: age, gender, anatomical site, histopathologic variant, sebaceous induction, follicular induction, epidermal change, and the presence of mitotic figures per 10 high-power fields (HPF).

In this study, we defined sebaceous induction as an increase in number of sebaceous lobules (at least more than two lobules) that they are not affiliated with a normal hair follicle. A short, rather distended sebaceous lobule away from the site of normal sebaceous gland is also considered as sebaceous induction. These changes are easily appreciated when the biopsy was taken from anatomical sites other than the face, it is difficult to interpret the enlarged or hyperplastic sebaceous gland in the face, therefore it was excluded from the study. Consulted cases in which the slides were no longer available were also excluded.

Microsoft Excel 2020 was used in our statistical analysis. The data (scores) had been entered into a Microsoft Excel 2020 worksheet and configured properly. Mean (\pm standard deviation) have been used to describe continuous variables (i.e. age). Count (frequency) have been used to describe other nominal variables (i.e. gender).

Results

One hundred consecutive NFs were evaluated from 100 patients, NFs were as common in females as males (male to female ratio 1: 1), 49 patient were male ,while 51 were female .The mean age was 64 ± 13.7 years (range, 14–91 years), with 47% diagnosed in between 60 and 80 years.(Table 1) The most common sites were the upper extremities (20%) and the back (16%) followed by abdomen (13%), chest (11%) and neck (11%). (Table 2) The detailed clinical history was not available for all cases.

The histopathological features that were observed in our slides include delicate wavy spindle cells embedded in a loose stroma composed of thin collagen bundles. The most common variant was extraneural sporadic cutaneous NF (95%), with only 3 cases of plexiform NF (3%) and 2 cases of diffuse NF (2%). No abnormal mitotic figures or necrosis were identified in all cases studied (figure 1).

Sebaceous induction was present in 22% of NFs with exclusion of NFs located on the face (forehead, chin, cheek, and nose) which constitute about 10 % of cases. The sites of distribution for NFs with sebaceous induction showed as follows: Upper extremities (3%), lower extremities (1%), chest (4%), back (5%), abdomen (3%), neck (4%), perianal (1%), ear lobe (1%), scalp (5%).

Table I: Age distribution of NF cases.

Age (years)	Number of cases
0-20	1
20-40	6
40-60	38
60-80	47

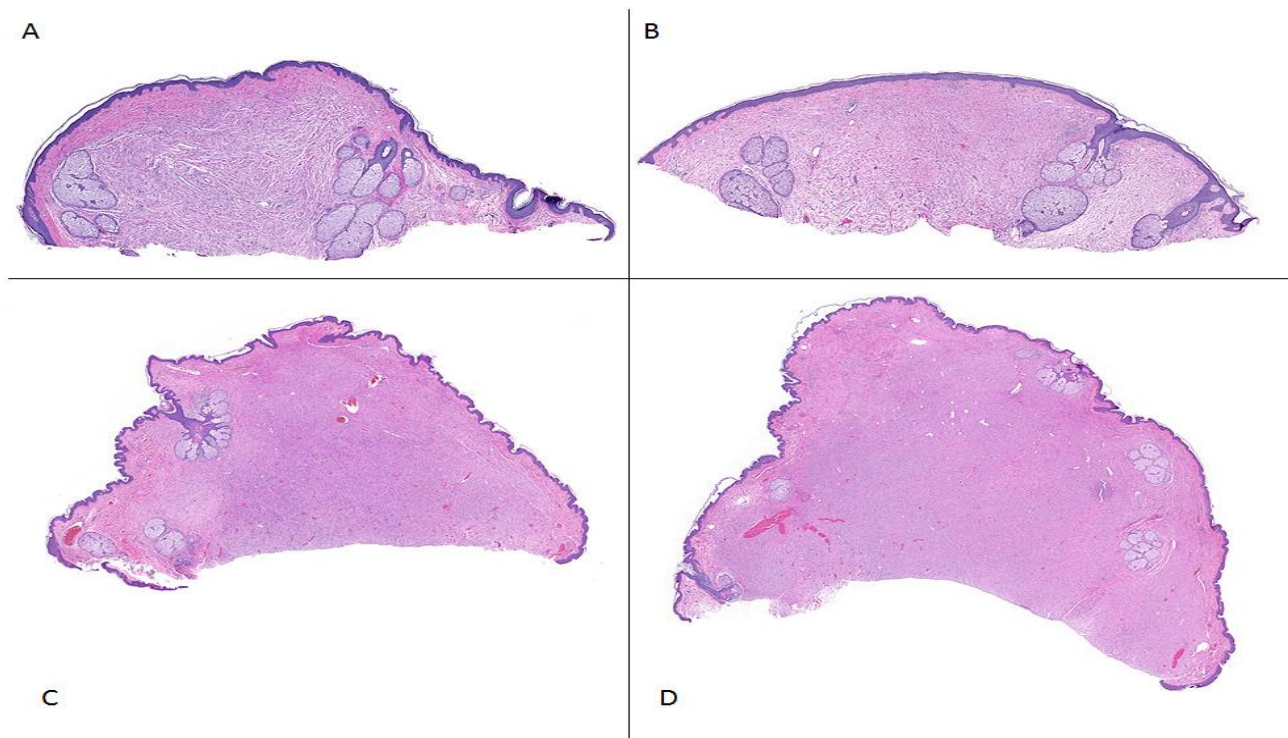
Above 80	8
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Table II: anatomic location of NF cases.

Anatomic location	Number of cases
Face	21
Upper extremities	15
Back	13
Abdomen	12
Chest	11
Scalp	8
Lower extremities	6
Neck	5
Perianal	5
Earlobe	4

Figure legends

Figure 1: Neurofibroma with sebaceous induction. Biopsy was taken from midback (A, H&E: 100x), perianal area (B,H&E: 100x), mid trunk (C,H&E: 20x) and Knee (D,H&E: 20x).



Discussion

In this study, we report sebaceous induction in a large series of NF that has not been studied before. Follicular induction has been mentioned as a phenomenon associated with a variety of lesions such as dermatofibromas, dermatofibrosarcoma protuberance, focal mucinosis, wart, seborrheic keratosis, neurofibroma, scar, angioma, nevus sebaceous, anetoderma, pilomatricoma and chronic lymphedema [5-8]. Sebaceous induction has also been mentioned in neurofibroma in a study done by Requena *et.al.*[9] However, they did not obtain the frequency of this phenomenon and also there is no any cross-sectional study in the literature after a thorough search. In our work, sebaceous induction was identified in 22% of our retrospectively cases and all reported cases fulfilled the criteria for sebaceous induction (more than two lobes, very superficial in location or not affiliated with hair follicle). The mean age in our study was 64 years somehow older for the development of NFs. [10] No gender predilection was found in our study. In contrast, in none of our cases studied, follicular induction was identified.

As a well-established phenomenon, epidermal, sebaceous and follicular induction has been frequently described in dermatofibroma. [5, 10-16] One study showed sebaceous and follicular induction is associated with dermatofibroma (especially the cellular variant) in 16% of cases.[6] In another large study, Shuweiter and Boer have showed sebaceous and follicular inductions are present in 31.6% of dermatofibromas. [17] They included mantle differentiation as a part of sebaceous induction in their assessment and this would be the reason why they reached to a higher percentage of induction by dermatofibromas compared with previous works. [17] Considering the above numbers in dermatofibromas, sebaceous induction in neurofibromas as 22% in our study should be interpreted as a common finding. However in none of our cases follicular induction was noticed.

In another study, follicular induction has been reported overlying one case of DFSP. [18] Following this finding, the authors reviewed all cases of DFSP for the previous eight years. In a total of 28 cases of DFSP studied by the authors, neither follicular nor sebaceous induction was identified. This is important, because sebaceous induction could be used as a histopathologic clue for diagnosing of neurofibroma in differential with DFSP. Moreover, Ackerman reviewed “induction of follicles” in different lesions in the skin and illustrated another case of DFSP that was associated with follicular induction. [19] In none of these two cases of DFSP,sebaceous induction was identified.

The etiology of underlying sebaceous induction in NF is unknown, but probably is similar to sebaceous induction in dermatofibroma where epidermal-mesenchymal cellular interactions, like induction, occur in response to injury with tissue repair. Epidermal growth factor (EGF) is one of the important soluble mediators which are known to stimulate the proliferation and differentiation of a variety of transformed and benign tissues. Expression of epidermal growth factor receptor (EGF-R) in dermal spindle cells and the epidermis has been suggested as a cause of sebaceous induction. [20] Other authors have suggested a role for Hedgehog pathway and beta-catenin in regulation of sebocyte development. Aberrant Hedgehog signaling results in formation of sebaceous glands in the areas of the skin that normally devoid of hair and associated structures, whereas low levels of beta-catenin stimulate sebaceous differentiation. [21].

We think in a similar way, the balance of these two pathways may influence whether or not sebaceous induction occurs in NFs, but the exact mechanism has not completely been elucidated.

Although the frequency of 22% is significant in our work, it should be supported by other studies and more samples to be fully considered as one histopathological clue for diagnosing of NFs.

Limitations

The findings of this study have to be seen in the light of some limitations. First, the detailed clinical history was not available for all cases; as in most retrospective studies. Therefore, we could not evaluate if there is any clinical implication or correlation for those patients who have NFs with sebaceous induction. Second, there is no any cross-sectional study in the literature after a thorough search. Therefore, we did not have the opportunity to compare our results with other studies. Further studies with larger sample size is needed to further elaborate the significance of this finding.

Conclusion

Sebaceous induction is an interesting and not uncommonly observed feature in NFs, not previously studied in a series of cases. On the other hand, follicular induction was not shown to be associated with neurofibromas.

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