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Superficial neurofibromas in the setting of schwannomatosis: nosologic implications

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Abstract

First described in the past decade, schwannomatosis is a syndrome distinct from neurofibromatosis 2 (NF2). It is characterized by the development of multiple schwannomas, sparing the vestibular division of cranial nerve VIII, and may also predispose to develop meningiomas. We report two female patients, a 27 and a 44 years old who developed multiple peripheral schwannomas, but without involvement of the vestibular nerves, satisfying clinical criteria for schwannomatosis. Lack of vestibular nerve involvement was confirmed with MRI using an internal auditory canal protocol with 3 mm thick slices in both patients after age 30. Both patients developed a small neurofibroma in axillary subcutaneous tissues and a diffuse cutaneous neurofibroma of the left buttock, respectively. This report highlights that superficial neurofibromas may arise in the setting of schwannomatosis, which may have implications for the diagnostic criteria of this unique syndrome. In particular, the presence of a cutaneous neurofibroma in a patient with multiple schwannomas should not lead to a diagnosis of NF2.

Keywords

Schwannoma; Neurofibroma; Schwannomatosis; Neurofibromatosis; Peripheral nerve

Introduction

The two principle forms of benign nerve sheath tumor are neurofibromas and schwannomas. Despite their favorable prognosis it is essential to differentiate them for three reasons: first, neurofibromas when involving nerve are less circumscribed and cause fusiform expansion which makes resection more challenging in comparison to the globular, more localized schwannomas; second, neurofibromas may undergo malignant transformation in a small percentage of cases (approximately 5% in plexiform examples) [4, 15], while such change in schwannomas remains a pathologic curiosity [17]; and third multiple tumors of both forms are associated with distinct syndromes, namely neurofibromas with neurofibromatosis type 1 (NF1) and schwannomas with neurofibromatosis type 2 (NF2), and with schwannomatosis. Schwannomatosis is a recently described form of neurofibromatosis, usually sporadic and prognostically more favorable than NF2, in which involvement of the vestibular nerve is lacking [10, 14]. In addition, schwannomatosis patients do not have *NF2* germline mutations and in some familial cases *SMARCB1* germline mutations have been found. Given some difficulties in distinguishing the two syndromes, consensus criteria based on the clinicopathologic features have been recently proposed [12]. However, there is variation in the timing and site of occurrence of schwannomas in some families, and some cases interpreted as representing familial schwannomatosis might indeed represent mosaic NF2 [5].

Although neurofibromas are a hallmark of NF1 and schwannomas are the hallmark of schwannomatosis and NF2, neurofibromas may occur in NF2. Their occurrence in this disorder in fact has been incorporated into the Manchester criteria along with other tumors these patients may develop [1, 6].

We report two patients that satisfy the proposed clinical criteria for schwannomatosis [12] who developed two small classic neurofibromas: one a subcutaneous neurofibroma in the axillary soft tissue (case 1); and the other a diffuse cutaneous neurofibroma (case 2). The clinicopathologic features of these cases are described and their relation to the diagnostic criteria of schwannomatosis is discussed.

Patients

Case 1—The patient, a 27-year-old right handed woman, was diagnosed with a “neurofibromatosis-like condition” at age 10. In a 10-year span, she underwent excision/resections of approximately 30 nerve sheath tumors involving mostly the left arm. There was no family history of nerve sheath tumors. A schwannoma laying in the pelvis adjacent to the inferior vena cava had been partially resected 7 years prior and did not involve the spinal canal. It had increased in size from 4 to 7 cm over the past years, but was clinically stable. A stable right retroperitoneal mass (T12–L3 levels) was also present.

Over a year her symptoms had progressed and she was experiencing daily severe pain which was no longer being palliated with medications. Neurologic exam disclosed decreased sensation to pinprick and light touch along the second digit, as well as hypersensitivity and allodynia on its volar aspect. Motor function was intact. Eye exam was normal and

specifically showed no cataracts or Lisch nodules. Skin exam was negative for café au lait spots. An MRI performed with an internal acoustic canal protocol with thin (3 mm) slices confirmed the absence of vestibular schwannomas on two separate occasions 2 years apart (at age 28 and 30). Surgical exploration of the left axillary level brachial plexus and upper extremity with neurolysis of the radial nerve, and resection of three tumors were performed (Fig. 1a). Two small tumors involving subcutaneous soft tissues of the left axilla were also removed. They did not form palpable cutaneous nodules. None of the lesions was plexiform in appearance.

Case 2—A 44-year-old woman underwent resection of three tumors, one each involving the left lower leg, left foot, and left buttock. She had pain in her left foot for about 4 years and then increasing pain and paresthesias of her left arm. The pain in the foot became widespread involving the lower left leg and then the entire left leg. MRI of her cervical spine showed widespread disc disease, otherwise unremarkable. MRI of the brain was unremarkable. MRI of the left foot showed three T2 hyperintense lesions, two in the left ankle (tibial nerve), and the second in the arch of the left foot. Physical examination revealed a single skin lesion in the left buttock. She had no café au lait spots. The patient underwent surgery and the skin lesion from the buttock, and two symptomatic lesions from the left ankle and foot were removed. After surgery, the pain in her foot has almost entirely resolved. MRI scan including thin cuts through the internal acoustic canal showed no masses on the eighth cranial nerve.

Materials and methods

H&E stained slides obtained from formalin-fixed paraffin embedded tissues were re-reviewed in case 1 and case 2. Immunohistochemical studies were performed using a Dako autostainer and the Dual Link Envision1 detection system with antibodies directed against S-100 protein (Dako, polyclonal; 1:800), smooth muscle actin (SMA) (Dako, clone 1A4; 1:150), epithelial membrane antigen (EMA) (Dako, clone E29; 1:20), desmin (Dako, clone DER11; 1:100), neurofilament protein (Dako, clone 2F11, 1:75), myogenin (Dako, clone F5D, 1:500), collagen IV (Dako, clone CIV22, 1:25), INI-1-BAF47 (clone 25, 1:100; BD transduction, BD Biosciences, San Jose, CA, USA), Ki67 antigen (Dako, clone MIB-1, monoclonal; 1:800), and p53 protein (Dako, clone DO-7; dilution 1:200).

Results

Pathology

Case 1—All tumors examined (except for the one described below) showed similar features. Grossly, they were lobulated and mucoid. Microscopically, they were composed of spindle cells arranged haphazardly or in short fascicles and nodules, with frequent Verocay bodies in Antoni A areas (Fig. 1b). There was mild to moderate pleomorphism with ancient change in areas. Antoni B tissue was also noted. Mild chronic inflammatory cells, vascular hyalinization, and portions of a capsule were also present. Proliferative activity ranged up to a maximum of 2 mitoses per 10/hpf. The neoplastic cells showed strong expression of S100 and collagen IV. EMA and neurofilament protein stains were mostly limited to the perineurium and to the subcapsular periphery of the tumors, respectively. In addition,

increased numbers of axons were noted in both small tumors of the axillary soft tissue, as well as in an Antoni B region in the largest axillary tumor.

One of the small axillary soft tissue tumors, a neurofibroma, consisted of small spindle cells with wavy nuclei accompanied by wisps of collagen, all immersed in a mucinous matrix (Fig. 1c, d). Scattered mast cells were also found. Both, hyalinized vessels and a well-developed capsule were lacking. Neurofilament stains highlighted numerous axons coursing within the substance of the tumor (Fig. 1e). These findings were diagnostic of conventional neurofibroma. INI1 immunostaining was present in the majority of tumor cells (90%) in both the schwannomas tested and the neurofibroma (Fig. 1f).

Case 2—The tumors examined measured $3 \times 2.3 \times 1.7$ cm (left lower leg), $2 \times 1.6 \times 1.1$ cm (left foot), and 0.9 cm (left buttock). All were grossly tan, nodular, and well circumscribed. Histologic examination of the left lower leg and left foot tumors demonstrated similar features, including solid aggregates of spindle cells with schwannian features and Verocay body formation in Antoni A areas (Fig. 2a). Thick hyalinized vessels were frequent. Prominent nodular zones featuring myxoid matrix were intermingled with Antoni A tissue (Fig. 2b). Mitotic figures were infrequent (<1 per 10 hpf). The neoplastic cells reacted strongly with S100 protein antibody. Neurofilament protein staining showed the tumors in large part to be architecturally solid, with rare neurofilament protein positive axons in the periphery, but not in the substance, of the tumors as typically noted in schwannomas.

Histologic examination of the left buttock skin lesion showed the dermal proliferation of benign spindle cells with elongate wavy nuclei and little discernible cytoplasm set in a fine collagenous matrix centered in the dermis. Myxoid changes were not present. Although the low power appearance gave an impression of circumscription (Fig. 2c), on higher power the neoplasm was seen to infiltrate among adnexal structures (Fig. 2d) as well as within connective tissue. Most, but not all neoplastic cells showed S100 protein immunoreactivity. Neurofilament protein immunostain highlighted small cutaneous nerves and rare axons within the tumor (Fig. 2e). These features were diagnostic of diffuse cutaneous neurofibroma. Interestingly in both the schwannoma tested and the diffuse neurofibroma, INI1 staining demonstrated patchy loss, or a mosaic pattern (staining 50–60% of tumor cells) similar to that described before in schwannomatosis tumors with INI1 loss [13].

Discussion

The clinicopathologic features of schwannomatosis, a multiple schwannoma syndrome, have been more accurately characterized in the past decade [10, 12]. Clinically, the disorder differs from NF2 in that it lacks vestibular schwannomas, ependymomas and ocular manifestations. Although initially meningiomas were thought to be a feature of NF2 only, recent reports suggest that schwannomatosis patients are predisposed to develop meningiomas as well. In most instances, established criteria permit a clear distinction between the two conditions [12].

NF2 and schwannomatosis are distinct at the molecular genetic level. In most instances, the underlying genetic defect in NF2 is a germline mutation in the *NF2* locus on chromosome 22. Efforts to identify a candidate gene for schwannomatosis have been undertaken in recent years [3]. In familial schwannomatosis, which represents approximately 15% of cases, the *NF2* locus has been excluded as being responsible for the disorder [11]. Furthermore, different schwannomas from the same patient and from different family members show different mutations of *NF2* [9]. More recently, some cases of familial schwannomatosis have been associated with the mutations in the tumor suppressor gene *INI1/SMARCB1* [2]. Most recently, germline mutations in this gene have been reported to occur in 33.3% of individuals with familial schwannomatosis and 7.1% of individuals with sporadic schwannomatosis [7]. A mosaic pattern of INI1 protein staining occurs in most schwannomas from familial schwannomatosis patients, and in 50% of schwannomas from sporadic schwannomatosis patients, suggestive of involvement of the *SMARCB1* gene in the pathogenesis of the disease [13]. It should be noted that a mosaic pattern of INI protein staining is seen in the majority of NF2-associated tumors (83%), therefore, it does not separate schwannomatosis from NF2-associated tumors.

Cutaneous neurofibromas are included among the various tumors that patients with NF2 develop in addition to schwannomas. Here, we report two patients fulfilling clinical criteria for the diagnosis of schwannomatosis. Although this may just be a random coincidence, as neurofibromas are common lesions in the sporadic, general population, it raises the possibility that cutaneous and subcutaneous neurofibromas may be a feature of schwannomatosis in a similar way that they are in NF2. As clinicians may use the presence of neurofibroma in a multiple schwannoma patient as a diagnostic tool to support the diagnosis of NF2, the occurrence of such lesions in the context of schwannomatosis is important to report. Until more cases of neurofibromas arising in the context of schwannomatosis become available, our report should be interpreted with caution since neurofibromas are common, sporadic neoplasms, and we cannot rule out that they represent a coincidental occurrence in these patients. However, the presence of a neurofibroma in a patient with multiple schwannomas should not support a diagnosis of NF1 or NF2.

In addition, this case also highlights the importance of accurate pathology in classification and clinical diagnosis of these patients. The histological classification of peripheral nerve sheath tumors in neurofibromatosis patients may be more difficult than in the general population as peculiar forms may be seen in association with these syndromes. Specifically, Poliani and colleagues identified several pathologic features associated with schwannomatosis, including prominent myxoid stroma which may mimic the growth pattern of a neurofibroma (unpublished data). In addition, embedded nerves [8] and axons (a feature commonly seen in neurofibromas) may be identified with neurofilament protein immunostains [16] in schwannomas associated with NF2 or schwannomatosis.

These findings indicate our incomplete understanding of the neurofibromatoses and reasonably prompt speculations regarding schwannomatosis, the newest addition to the disease spectrum. The clinical, histopathologic, and molecular aspects of this uncommon syndrome continue to evolve, as do criteria developed for its recognition and necessary separation from related, more ominous multitumor syndromes.

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Fig. 1. Case 1. Multiple schwannomas demonstrated during surgery in the axillary region (**a**). Classic schwannoma histology including frequent Verocay bodies in Antoni A areas, and a focus of loose mucoid Antoni B (**b**). A small neurofibroma was found in the subcutaneous tissues (**c**), containing wavy cells and wispy collagen fibers (**d**). Immunohistochemical stains demonstrated scattered internal axons (**e**) while INI1 expression was retained in the majority of the neurofibroma cells

Fig. 2. Case 2. Multiple myxoid schwannomas were the predominant histologic feature (**a**, **b**). A separate buttock lesion showed conspicuous dermal infiltration characteristic of diffuse neurofibroma (**c**, **d**). Immunohistochemical stains demonstrated scant internal axons (**e**). Immunohistochemical stain for INI1 showed patchy loss in neurofibroma cells as previously described in schwannomatosis-associated tumors (**f**)