CASE REPORT

Periarticular diffuse neurofibroma of the upper limb

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Abstract

The diffuse neurofibroma is an uncommon subtype of neurofibroma that has received little attention in the imaging literature. Most common in ages 10–30, in males and females, with a slight predilection for the trunk, then head and neck, then limbs. May become very large, but very rarely undergo malignant transformation. Treatment of diffuse neurofibromas (not associated with NF1) is often surgical resection. Complete resection is often difficult because of the extensive and infiltrative nature of many of these lesions. To our knowledge, the diffuse neurofibroma has been reported extremely rarely within the shoulder girdle. In this report, we presented an adult patient, without NF1 diagnosed, who developed invalidate status of left upper limb due to a giant diffuse neurofibroma involving the left brachial plexus, with a high growth diffuse pattern and plexiform architecture imagistic, grossly and without results at both surgical interventions. The diagnosed was by MRI and sonographic imaging and histopathologic examination. His immediately survival perspective was not affected but the functionality of the left upper limb was severe reduced.

Keywords: diffuse neurofibroma, upper limb, histopathologic examination, immunohistochemistry, Ki67.

Introduction

Classically, benign peripheral nerve sheath tumors (PNSTs) have been divided into neurilemmoma (schwannoma) and neurofibroma [1].

Neurofibroma most commonly affects patients of 20–40-year-old, childhood/puberty in NF1 and has male sex predilection [2]. Neurofibroma is common, representing approximately 5% of all benign soft-tissue tumors in large surgical series. Three types of neurofibromas are classically described: localized, diffuse, and plexiform (discussed with neurofibromatosis type 1 – NF1) [3, 4]. The microscopic findings are: cellular and stromal milieu (Schwann, perineurial hybrid, intraneural fibroblasts, mast cells, collagen bundles, and myxoid change); increased cellularity at center of neurofibroma compared with edematous periphery [2].

Diffuse neurofibroma is an uncommon subtype of neurofibroma that has received little attention in the imaging literature. It has been reported to occur most commonly among children and young adults, typically involving the skin and subcutaneous tissues of the head and neck [5–10]. Most common in ages 10–30, in males and females, with a slight predilection for the trunk, then head and neck, then limbs. May become very large, but very rarely undergo malignant transformation. The majority of diffuse neurofibromas (90%) are isolated lesions not associated with NF1 [3, 5, 6, 9–12].

At gross examination, unlike other types of neurofibroma, which have a masslike pattern of growth, diffuse neurofibroma is a poorly defined lesion in the subcutaneous fat that spreads along connective tissue septa and surrounds rather than destroys adjacent normal structures. These tumors are intimately intermixed and are inseparable from normal nerve tissue [3, 6, 9, 10]. Nerves or nerve fibers within the lesion tend to be markedly hypertrophic and edematous. It is not uncommon to see pigmented dendritic cells. There may be rare multinucleate giant cells [13].

At histologic analysis, unlike neurilemmoma, neurofibromas do not contain Antoni A and B regions [13–15]. Myxoid areas and degenerative regions are also not as prominent as they are in neurilemmoma. A neurofibroma is a mass that represents coordinated hyperplasia, not simply the clonal proliferation of one cell type. This mass contains multiple cell types-Schwann cells, perineurial cells, nonspecific fibroblasts, endoneurial fibroblasts, endothelial cells, mast cells, and sometimes adipocytes, smooth muscle cells, melanocytes, and hair cells and as well large amounts of intercellular material, including collagen (very uniform, prominent fibrillary collagen) and amorphous ground substance, for example, mucopolysaccharides and glycosaminoglycans [16].

Diffuse neurofibromas are positive for S100 protein at immunohistochemical analysis, although generally not as extensively as neurilemmoma [13].

Treatment of diffuse neurofibromas (not associated with NF1) is often surgical resection. Resection is performed when the tumor is severely disfiguring or
severely compromises function [17]. Complete resection is often difficult because of the extensive and infiltrative nature of many of these lesions [4, 6, 11, 17]. Unlike neurilemmoma, however, neurofibromas cannot be separated from normal nerve, and complete excision of the neoplasm requires sacrifice of the nerve. Local recurrence after complete excision is unusual and is more frequently associated with diffuse neurofibroma because of its infiltrative growth. Malignant transformation of these lesions, without association to NF1, is rare and not well documented in the literature [5, 13–15].

The realistic expectations concerning surgical treatment of neurofibroma must take into account the type of neurofibroma and the anatomical location, the extent of compromise already present at the time of surgery, and the potential adverse outcomes, including anesthesia, dysesthesia, and/or motor deficits [16].

Shoulder pain is a common presenting symptom and may be secondary to a variety of underlying causes. We report a case of shoulder pain and severe disability of upper limb caused by a periarticular diffuse neurofibroma. To our knowledge, the diffuse neurofibroma has been reported extremely rarely within the shoulder girdle [18].

🎉 Patient, Methods and Results

We report a case of a diffuse neurofibroma on the girdle of left upper limb in an adult man, confirmed by MRI and ultrasonography imaging as well as histopathology examination.

History

A 55-year-old man without history of disorders presented in the Rehabilitation Department (RD) with a ten months history of atraumatic pain in the left shoulder. The pain was insidious in onset, diffuse and dull, non-radiating, and unprogressive. His pain has been worsening over the last two months, with associated progressive swelling of the infraclavicular region. The patient reported that his pain was absent while resting, being accentuated during nights, while lying on his homonym side, as well as with any activity, particularly when lifting his arm (with and without weight).

Constitutional symptoms were absent, as were proximal pain or neurological symptoms. The patient denied any recent heavy lifting or trauma. He also denied fever or warmth of the left shoulder; had no allergies to medication and denied any tobacco, alcohol, and illicit drug use. The family history was noncontributory.

Clinical examination

The physical examination revealed a well-appearing, middle-aged man in no acute distress. His temperature was 36.8°C, blood pressure 130/80 mmHg, heart rate 76 beats/min, and respiratory rate 20 breaths/min.

On examination of the left shoulder, we could observe a large, tense superficial formation measuring three by four centimeters. We found significant tenderness upon palpation of the area. The skin was intact and we could not identify erythema or warmth of the shoulder area. Rotation of the shoulder was impaired because of the pain (especially internal rotation), and we observed weakness while testing the subscapular muscle. The patient was unable to lift his left arm past 100° of forward flexion or 70° abduction without experiencing severe pain. The distal motor, sensation, and reflex examinations were otherwise unremarkable. The extremity pulses were normal.

The patient was given oral analgesics for pain control. The left shoulder radiograph did not demonstrate any fracture. Laboratory examinations demonstrated normal values of the C-reactive protein, erythrocyte sedimentation rate and complete blood count.

General examination revealed no Lisch nodules or other findings suggestive of a diagnosis of neurofibromatosis. Physical and mental development showed no abnormalities and a diagnosis of Von Recklinghausen’s neurofibromatosis (NF1) could not be established.

🔍 Imagistic evaluation

Ultrasoundography was consistent with other findings of soft tissue diffuse neurofibromas; the lesion (with dimensions of 20×19×16 mm) was located in the subcutaneous fatty zone, had poorly defined margins with normal adjacent subcutaneous muscular tissue and fat deposits. The mass was hyperechoic with multiple small interconnecting irregular hypoechoic areas (nodular structures) (Figure 1).

Figure 1 – Ultrasound aspect of tumoral mass in left shoulder girdle.

The orthopedic surgeon recommended obtaining a magnetic resonance imaging (MRI) scan of the left shoulder (Figure 2) to provide further information on the shoulder mass.

The MRI left shoulder examination in native and post-contrast incidences revealed a homogenous, moderately vascularized tumoral mass, measuring 10 by 6.5 cm, situated in the infraclavicular retro peritoneal area. It presented a lobular, triangular aspect, being situated behind the left pectoralis muscle, below the clavicle, anterior of the left scapula and laterally from the ribcage, further spreading into the left axillary region, in close contact and segmentary inclusion of subclavicular blood vessels and elements of the brachial plexus. A two centimeter parcel area of enhanced osseous signal with cortical effraction was also observed, possibly indicating osteolysis or pressure atrophy.
Periarticular diffuse neurofibroma of the upper limb

Figure 2 – Coronary section. Neurofibroma of the axillary left region. (A) – Native T2 sequence showing a multi-lobulated mass in the axillary region with heterogeneous T2 hyperenhancement, exhibiting a compressive effect on vascular and nervous adjacent structures; (B) – Post-contrast pondered T1 section, we could distinguish homogeneous intense hyper enhancement of the tumor mass.

These examinations suggested that the tumor mass interested the anatomical structures of the left upper limb girdle. Surgical excision was performed for definite diagnosis and treatment. The macroscopic appearance of the tumor was of an irregularly multi-lobulated mass (nine fragments with dimensions between 1.5 and 5.5 by 2 cm diameter – Figure 3), grayish in color, with secondary degenerative changes and firm consistency.

Figure 3 – One fragment of an irregularly multi-lobulated mass tumor: smooth-surfaced mass, 1.5×2 cm diameter, with firm consistency, grayish in color with secondary degenerative changes.

Histological examination of the tumor biopsy (Hematoxylin–Eosin stained section) showed a microscopic structure common to a neurofibroma, with the presence of microcalcifications, hemosiderinic pigment, dense collagen stroma with hyaline and myxoid areas. Histological examination demonstrated an ill-defined, infiltrative lesion occupying the subcutaneous tissue without destroying the skin appendages.

We also found interlacing bundles of elongated cells. The cells were fusiform, with elongated nuclei, surrounded by a myxoid matrix with wire-like collagen fibers. No Meissner bodies were seen.

The lesion was characterized by a proliferation of spindle cells that contained elongated ovoid nuclei, surrounded by a matrix with wire-like collagen fibers (Figure 4).

Immunostaining completed the pathology examination, paraffin embedded tissue blocks being immunostained by using the three-step Avidin–Biotin Complex method (ABC method). The lesion was positive for S100 protein antibody. Immunoperoxidase staining with S100 protein showed positive staining of the nuclei and cytoplasm of the tumor cells (Figure 5).

The positive diagnosis diffuse of neurofibroma of left girdle of upper limb was based on the patient history, clinical findings, and imagistic investigations and especially on the histological exam of the tumor after surgical resection. The patient underwent a supervised rehabilitation program following surgery – TENS, massage and kinetic exercises, focused on regaining the functionality of the upper limb (ADLs normalized and social reintegration).

The evolution was not satisfactory, his neurological signs altering progressively. He presented superficial sensory alterations, motor deficits, and diffused pain in entire upper limb. As the mass moved concomitant to the joint, we suggested that there was an attachment to the joint capsule or surrounding muscles. These unfavorable symptoms were sustained by the results of EMG exam – amplitude of signal was diminished in the left limb compared with the right side, and the latency was more prolonged in left limb (Figure 6a) compared with the right side (Figure 6b).

Figure 4 – Neurofibroma with fine fibrillary collagen matrix and fusiform cells with hyperchromic nuclei. HE stain, 100×.

Figure 5 – Neurofibroma, diffuse positive immunostaining for the S100 protein. LSAB technique, 200×.

After clinical and imagistic (ultrasonography and
MRI – Figure 7) follow-up, eleven months later, we concluded that tumor mass had significant recidivated and another surgical intervention was performed.

Figure 7 – (A) Axial section; (B) Sagittal section. We could observe a tumor mass and its relation with adjacent structures, including anomalies in the scapular and left clavicle areas, signifying atrophic foci after compression or focal demineralization.

The second MRI showed a residual tumor mass with enlarged dimensions (19 cm in the long axis of reconstructed images in the coronary plane). It had a multilobular aspect with subclavicular extension towards the left scapulohumeral joint and the disappearance of the cleavage space with the joint capsule. Nodular images with hypoenhancement at clavicle and scapular level, suggestive to contiguity extension. We noticed the disappearance of the cleavage space with the rib cage, extension and merger of the brachial plexus components. The formation showed relatively homogenous enhancement. Also, we could observe adenopathies in the supraclavicular fossa.

The histological aspects described in the second excision tumor were of a diffuse proliferation of spindle cells arranged in fascicles, reduced inflammatory reactivity with areas of collagen fibrosis, aspect characteristic for diffuse neurofibroma. Immunohistochemistry showed positive reaction to desmin in microfibroblastic cells, positive S100, positive alpha-actin in blood vessels, negative CD117, positive CD31 in vessels, however negative inside the tumor, positive CD34 for vessels and intensely positive VIM. The pathology and immunohistochemistry was relevant for fibromatosis (Figures 8 and 9).

Figure 8 – Neurofibroma, positive CD34 staining in fibroblast-like cells. LSAB technique, 100x.

Figure 9 – Neurofibroma, rare CD57 positive cells. LSAB technique, 200x.

Differential diagnosis was performed with other tumor masses – schwannoma, malign peripheral nerve sheath tumor (MPNST), benign fibrous histiocytoma, desmoplastic malignant melanoma.

After the second surgical intervention, the evolution had the same unfavorable pattern. These aspects and imagistic exploration indicated the need for aggressive resection.

The particularity of our case was the giant neurofibroma of left girdle upper limb in an adult man without NF1 diagnosed, with a high growth diffuse pattern and plexiform architecture, grossly and without results after both surgical interventions. The peripheral nerve tumor presented initially as a painless lump, otherwise asymptomatic; the diffuse neurofibroma of our patient might have been very large before it produced a notable mass. The residual tumor mass had a relationship to the clavicle and attachment to the surrounding structures; when finally it was palpated, we determined the morphological characteristics (the smooth surface of the lobulated tumor; the edges of tumor were irregular and poorly defined), having a soft consistency. The overlying and surrounding skin had no modifications (discoloration, necrosis, or associated lesions). The motor deficits were a late sign; the patient described the deficit in terms of general movements or a functional impairment (he complained to have difficulties with buttons, knitting, and opening containers, having to switch to the non-dominant hand to perform certain tasks). The Tinel sign was positive and the Horner syndrome was absent.

His immediately survival perspective was not affected; however the functionality of the left upper limb was severely reduced. This tumor can become malignant; it is heralded by rapid growth and pain, by MRI aspects. PET scans may be used to help exclude malignancy.

Discussion

In this report, we presented a patient who developed invalidating status of left upper limb due to a giant diffuse neurofibroma involving the left brachial plexus. Our patient was integrated in the redefined
demographic characteristics of patients diagnosed with neurofibroma; in the last years, the neurofibroma (without NF1) has been reported to occur not only in children and young adults, but also after 40-year-old. Diffuse neurofibroma affects a wider age range of patients than previously believed [19, 20].

The described neurofibroma was localized at the level of the girdle of the upper limb, and crossed tissue boundaries (muscle, bone, vascular and nerve tissues). This aspect is in accordance with the conclusion of other studies: although the head and neck region has been previously described as the most typical site, in recent studies, trunk and extremity lesions were more common, each accounting for slightly more than one third of all diffuse neurofibromas [19, 20].

Before histological examination offered by the surgical department, the complete clinical and functional patient evaluation was an important aid to diagnosis. Similar to other neurofibromas studies, in the first clinical examination, our patient presented pain, paresthesias—manipulation of the mass produced paresthesias in the left shoulder and arm, numbness and an enlarging firm palpable mass and minimal neurological [21].

After six months, our patient had complained about the enlarging infracavicular palpable mass, pain, paresthesias and progressive neurological deficit in left upper limb. First, the tumor had medium dimensions of 6.5 by 10 cm and after the second evaluation; the tumor was larger than 15 cm.

Histologically, the majority of neurofibromas are part of the common type, being composed of interlaced fascicles of elongated cells with oval nuclei, tachichromic, thin collagen fibers and mucous material in variable quantities. One can observe lymphocytes, mastocytes and rare xantomatous cells [20]. As neural benign tumors, neurofibromas can present one of the three growing patterns: localized, diffuse and plexiform.

Based on histology, our studied neurofibroma was of a diffuse type, one of the three distinguished types of neurofibroma: localized, plexiform, and diffuse types. Diffuse neurofibroma is an ill-defined infiltrative lesion and tends to involve the skin and subcutaneous tissues. Though about 10% of patients with diffuse neurofibromas also have associated neurofibromatosis [1], in our study this aspect was not confirmed [20]. Diffuse neurofibroma consists of small round to spindled cells, with an associated fibrillar and myxoid background, which infiltrate subcutaneous fat in a honeycomb pattern, reminiscent of dermatofibrosarcoma protuberans. Wagner–Meissner bodies are the hallmark morphologic characteristic of diffuse neurofibroma. Plexiform neurofibroma demonstrates plexiform architecture radiologically, grossly, and microscopically, with multiple intraneural nodules of tumor separated by epineurium and stroma. It can involve the subcutis or skeletal structure, or both. Both plexiform and diffuse patterns can be seen together [2].

Taking into consideration the four dominant growth patterns of neurofibroma (plaque-like, infiltrative, mass-like, or mixed), the studied tumor was infiltrative because the lesions had poorly defined margins and areas of interposed uninvolved tissue.

The myxoid described lesions represented a possible co-existing plexiform pattern neurofibroma.

Benign tumors of peripheral nerves, even though they have common origin from the neural crest, present a notable microscopic heterogeneity. Differential diagnosis of these tumors can sometimes be difficult on Hematoxylin–Eosin stained sections, cases when immunohistochemical examination can aid to the final diagnosis.

Neurofibromas have a distinctive immunoprofile, with multiple cell populations. The majority of cells within a neurofibroma express the S100 protein (Schwann cells), with a minority of cells expressing CD34 (perineurial fibroblasts). Residual axons may be demonstrated, on occasion, with neurofilament protein immunostains. Loss of S100 protein expression in areas worrisome for malignant change may be a useful adjunctive finding on occasion. Large, deep neurofibromas may occasionally be confused with low-grade fibromyxoid sarcoma but lack the whirling growth pattern, curvilinear vessels, and abrupt transition into myxoid nodules seen in the latter lesion. Diffuse neurofibromas should be distinguished from Dermatofibrosarcoma protuberans, which is composed of slender CD34-positive, S100 protein-negative, spindled cells arranged in a prominent storiform pattern. Plexiform neurofibromas may be confused with plexiform schwannomas; the latter lesions are typically much smaller, uniformly S100 protein-positive, and contain areas of solid Antoni growth.

In our study, we evaluated tumor cells immunostainings for the S100 protein, CD57, CD34 and neurofilaments, while tumor proliferation was quantified by Ki67 proliferation index. The studied tumor showed positive nuclear and cytoplasmic immunostaining for the S100 protein in the elongated fusiform cells. Immunostaining for neurofilaments was diffusely positive. Immunoreactivity for the CD57 marker was positive in few tumor cells, and the CD34 marker showed positive immunoreactivity in the cytoplasm of fibroblast-like cells of myxoid areas and peripheral tumors (cells with dendritic cytoplasmic processes relatively long, oval or round nuclei with fine chromatin). The value of Ki67 expression increased by 5% in tumor cell nuclei, mitotic activity correlated with increased, suggesting an early malignant transformation in our patient the tumor.

We performed ultrasonography in our patient, taking into the consideration the advantages of this increasingly used examination of the soft-tissue masses: wide availability, lack of ionizing radiation, cost-effectiveness, and speed of examination [22]. As are most superficial lesions, diffuse neurofibroma is often evaluated clinically [19]. The both sonographic aspects (echogenicity, location, margin) described in our patient were similarly with the other sonographic findings of soft tissue diffuse neurofibromas – the lesions were located in the subcutaneous fat zone, had poorly defined margins with adjacent normal subcutaneous fat and the adjacent muscles; the described mass was hyperechoic.
with multiple small interconnecting irregular hypoechoic areas (nodular structures) [23]. Sonography, however, was limited in assessment of the extent of large lesions and in discerning lesion margins. We did not performed high-resolution and color Doppler ultrasonography.

The magnetic resonance imaging (MRI) examination was necessary for the correct diagnosis and guide attitude in the surgical measures. MRI is the most important modality in the evaluation of NSTs to determine the location, margins, and the relationships of the tumors to adjacent structures, and differentiating between intraneural and perineural masses. MRI revealing an extensive diffuse neurofibroma that has replaced the muscle structures of left girdle upper limb. The MRI signal intensity characteristics of described tumor are similar to those described in previous case reports. Most diffuse neurofibromas were isointense or mildly hyperintense in relation to muscle on T1-weighted images and mildly or markedly hyperintense to muscle on T2-weighted images. Intense enhancement on contrast-enhanced images and prominent internal vascularity were common finding in our presentation and has been previously reported [24].

Differentiation of benign described tumor from malignant peripheral nerve sheath tumor is also often very difficult. On the other side, diffuse type of neurofibroma can be locally recurrent [2].

The present case is discordant with the belief that malignant transformation of diffuse neurofibroma is rare [6]. The following aspects: large size (>15 cm), enhancement vascularity, infiltrative margins, marked heterogeneity, rapid growth are suggestive features of malignancy. Recognition of these imaging features is important for prospective diagnosis and to help guide therapy in the clinical management.

Complete resection was quite difficult due to invasion of the tumor into the surrounding soft tissues (vital nerves, vessels) and joints. The tumor has irritated nearby nerves, and it was partially removed. This surgical aspect is in accordance with the previous surgical peripheral nerve tumor experiences: although schwannomas can usually be separated from the parent nerve and removed, it is often very difficult to do the same with neurofibromas [25].

Finally, the surgical intervention was not with curative aim, because the tumor had intimate contact with vessels and brachial plexus, and crossed bone boundaries (clavicula and ribs). The last pathological diagnosis after examination of resection fragment specimen together with the clinical course had guided further therapy.

**Therapeutic options for our patient**

Recent discoveries in the laboratory have clarified an understanding of the molecular mechanisms underlying the pathogenesis of benign peripheral nerve tumors.

Recognition of the causative roles played by neurofibromin and merlin at the NF1 and NF2 loci has served a crucial role in further developing an understanding of the molecular pathogenesis of neurofibromas, schwannomas, and MPNSTs.

Similarly, the mechanisms whereby idiopathic and syndromic (NF1- and NF2-associated) nerve sheath tumors progress to malignancy are being elucidated. This detailed understanding of the molecular pathogenesis of peripheral nerve tumors provides the information necessary to create a new generation of therapies tailored specifically to the prevention, cessation, or reversal of pathological conditions at the fundamental level of dysfunction [26, 27].

Recent advances in understanding of the molecular mechanisms subservient tumor formation and malignant progression provide the potential for targeted, pathway-specific interventions. Specifically, targets within the microenvironment include: mast cells, neoangiogenesis, and tumor-related fibrosis. In addition to altering the tumor phenotype, modification of the microenvironment holds the potential to generate a milieu that is less permissive to further tumorigenesis or malignant progression.

Current surgical therapy is largely effective for isolated neurofibromas and schwannomas. Near-term surgical advances will probably involve incorporation of minimally invasive methods of impeding tumor progression, which would permit the treatment of a larger number of suspicious lesions. Such a technique could also be applied to the difficult challenge of treating large plexiform neurofibromas in otherwise functional nerves [26].

**Conclusions**

Our studied tumor was a giant neurofibroma with complex findings, such as a deep diffuse neurofibroma with plexiform form – on the basis of histology (growth pattern) and imagistic aspects; the NF1 was not mentioned; we found a significant functional impact on the left upper limb in an adult active man while being impossible to be completely resected due to invasion of the tumor into the surrounding soft tissues (vital nerves, vessels), bone structures and joints.

The S100 protein was a correct choice, as it is necessary during the immunohistochemical diagnosis of peripheral nerve tumors. This benign tumor presented a Ki67 proliferative index of 5%. Taking account that the index is useful in differentiating an atypical neurofibroma from a malign tumor of a peripheral nerve sheath with a low malignancy index, we consider that the studied neurofibroma had an important malignancy grade. Our patient had to undergo periodical complete evaluations (clinical, functional and imagistic assessments) and counseled concerning radical surgical intervention in the possible malignant transformation.

Today, further advances in our understanding of the molecular and genetic pathogenesis of peripheral nerve sheath tumors may hold even more rational approaches to the management of these tumors, perhaps even without surgery.

**References**


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