

The Neural Pleonastics- Neurofibroma

Anubha Bajaj

Histopathologist in A.B. Diagnostics, New Delhi, India

Correspondence should be addressed to Anubha Bajaj, anubha.bajaj@gmail.com

Received: November 6, 2020; Accepted: November 24, 2020; Published: November, 2020

ABSTRACT

Neurofibroma is a common, benign, peripheral nerve sheath tumour composed of Schwann cells, fibroblasts, perineurial cells and mast cells enmeshed within a myxo-collagenous stroma. Majority (90%) of neurofibromas is sporadic and around 10% lesions are associated with neurofibromatosis type 1. Sporadic and syndromic neurofibromas emerge due to chromosomal deletion within neurofibromatosis 1 (NF1) gene. Tumefaction emerges as a soft, flesh coloured papule or miniature subcutaneous nodule. The neoplasm is composed of interlacing fascicles of elongated cells with wavy, darkly- stained nuclei admixed with innumerable mast cells and stromal collagen bundles. Neurofibroma is intensely immune reactive to S100 protein, SOX10, collagen type IV and fingerprint-like, immune reactive CD34. Neurofibroma mandates a segregation from malignant peripheral nerve sheath tumour, schwannoma, perineuroma, dermato-fibroma, dermato-fibrosarcoma protuberans, palisaded encapsulated neuroma, superficial leiomyoma, neurotized melanocytic nevus, ganglioneuroma, plexiform fibrohistiocytic tumour, nerve sheath myxoma, desmoplastic melanoma and neuro-thekeoma. Enlarged lesions require tissue evaluation and/or assessment with computerized tomography (CT) or magnetic resonance imaging (MRI). Comprehensive surgical excision is a preferred treatment strategy.

KEYWORDS

Schwann cells; Perineurium; Neurofibromatosis type 1

PREFACE

Neurofibroma is a fairly prevalent, benign, peripheral nerve sheath tumour composed of Schwann cells, fibroblasts, perineurial cells and mast cells disseminated within a variably myxoid or collagenous stroma. Neuronal element of transformed Schwann cells is admixed with non- neoplastic, fibrous element constituted of fibroblasts. Neurofibroma is generally engendered by chromosomal mutations within the neurofibromatosis 1 (NF1) gene.

DISEASE CHARACTERISTICS

Majority (90%) of neurofibromas is sporadic and demonstrates a minimal possibility of malignant metamorphoses. An estimated 10% of lesions are associated with neurofibromatosis type 1 (NF1) or neurofibromatosis type 2 (NF2) disorder. Superficial neurofibroma is a common entity, in contrast to deep-seated neurofibroma [1,2].

Neurofibroma is subcategorized into:

- Localized neurofibroma
- Diffuse neurofibroma
- Plexiform neurofibroma

Citation: Anubha Bajaj, The Neural Pleonastics- Neurofibroma. J Med Biol 4(1): 1-8.

© 2021 Tridha Scholars

As a frequently discerned neoplasm of peripheral nerve sheath, neurofibroma is devoid of gender, racial or ethnic preferences. Males and females are equally incriminated [1,2]. Localized neurofibromas are commonly discerned in adults between 20 years to 40 years although a variable age of disease onset is encountered. Diffuse and

Plexiform neurofibroma is frequently encountered in children although plexiform neurofibroma is exceptional beyond 5 years. Plexiform neurofibroma is a pathognomonic constituent of neurofibromatosis type 1 (NF1) and delineates an enhanced probability of malignant metamorphosis [1,2]. Neurofibroma can arise within the nerve, a lesion which is denominated as intraneural localized neurofibroma. Pacinian neurofibroma is an exceptional neoplasm representing cellular proliferation with occurrence of articulations akin to Vater-Pacini corpuscles. Vater-Pacini corpuscle is designated as a cutaneous mechanoreceptor initiating sensitivity to pain and pressure [1,2]. Pigmented neurofibroma is an exceptional neoplasm composed of disseminated, melanin-laden cells and benign neural cells. Pigmented variant comprises of around 1% to 5% of neurofibromas [1,2].

Disease pathogenesis

Sporadic and syndromic instances of neurofibroma emerge on account of chromosomal deletion within neurofibromatosis 1 (NF1) gene. Sporadic neurofibromas depict NF1 genomic mutation within the tumor cells. Syndromic neurofibromas appear due to germ line mutation of NF1 gene which encodes tumor suppressor protein, designated as neurofibromin, situated upon chromosome 17q11.2 [2,3]. Neurofibroma occurs on account of bi-allelic inactivation of tumor suppressor, neurofibromatosis type I gene situated upon chromosome 17q11.2. Non myelinating Schwann cell progenitors, immune reactive to p75, are a predominant component of neurofibromatosis type I. Plexiform neurofibroma depicts a paucity of non myelinating Schwann cells.

Dermal neurofibroma can depict non Schwann-cell like precursors of neural stem cell or progenitor cell [2,3]. Of obscure genesis, tumefaction arises from endoneurium and connective tissue enveloping peripheral nerve sheath. Tumor cells are immune reactive to CD34 whereas neural cells are immune reactive to S100 protein [3,4].

Clinical elucidation

The neoplasm often appears as a soft, flesh coloured papule or miniature subcutaneous nodule. Subjects are commonly asymptomatic. However, irritation, mild pruritus, pain or paraesthesia can occur with cosmetic affliction. Clinical manifestations pertain to variant of neurofibroma [3]. Localized lesions arise as painless, flesh coloured, violaceous papule, nodule or subcutaneous mass and can be misinterpreted as a nevus or achrochordon. Typically, solitary lesions are below < 2 centimeters with a palpable "buttonhole sign". Localized neurofibroma depicts a predilection for trunk, head, neck, and extremities although no site of tumor emergence is exempt. Localized, superficial neurofibromas are evenly disseminated upon diverse body surfaces [3,4]. Sporadic or localized variant of neurofibroma, emerging in absence of mutated neurofibromatosis type I gene, is a painless, gradually progressive, solitary, flesh coloured, soft, flaccid, rubbery, firm papule or nodule of variable magnitude of up to 2 centimeters and a smooth extraneous surface. Cutaneous or subcutaneous neurofibromas arise as a component of neurofibromatosis type I (NF1) disorder [3,4]. Diffuse neurofibromatosis commonly appears within head and neck and manifest as ill-defined, indurated plaques with thickened, adjacent cutaneous surface. Enlarged lesions demonstrate mild numbness or tingling [4]. Plexiform neurofibroma is enlarged, circumscribes multiple and major nerve fascicles and commonly emerges upon the head and neck, trunk or extremities. Superficial lesions appear as flesh coloured or hyper-pigmented nodules. Deep-seated lesions

emerging from spinal nerve roots are irregular, tortuous and manifest pain, numbness, paraesthesia, nodule formation and spinal nerve compression [3,4]. Inherited, diffuse or plexiform neurofibromas are associated with neurofibromatosis type I and demonstrate pertinent symptoms such as chronic pain, cosmetic disfigurement, social stigma and anxiety. Exceptionally, neurofibromatosis neuropathy can emerge due to endoneurial fibrosis with altered concurrence between Schwann cells and collagen fibrils [3,4]. Neurofibromatosis type I is appropriately categorized with concurrence of two or more of following criterion:

- ≥ 6 café au lait patches exceeding >0.5 centimeters in pre-pubertal individuals or >1.5 centimeters in post-pubertal individuals
- ≥ 2 neurofibroma of a particular variant or a singular plexiform neurofibroma
- Axillary or inguinal freckling
- ≥ 2 Lisch nodules
- Optic glioma
- Sphenoid dysplasia or cortical thinning of long bones in combination with or absence of pseudo-arthritis.
- First degree relative with neurofibromatosis type I [3,4]

Histological elucidation

Grossly, the neoplasm is elliptical, fusiform, encapsulated, well circumscribed, firm, grey/white, tan or flesh coloured nodule. Cut surface is pale, gelatinous, glistening, tan or grey/white. Localized neurofibroma appears as a fusiform nodule with foci of myxoid and cystic degeneration. Neurofibroma emerging from major nerve trunks is encapsulated with fusiform expansion of implicated nerve [4,5]. Neurofibroma of miniature nerves is well circumscribed and un-encapsulated. Deep-seated neoplasms can engender tortuous enlargement of peripheral nerves with consequent emergence of plexiform neurofibroma. Areas of degeneration, necrosis or haemorrhage are absent. Intersected, adherent nerve fibres appear as a component of the neoplasm [4,5]. Well circumscribed, localized neurofibroma is situated within the dermis or subcutaneous tissue. Dermal lesions are

typically un-encapsulated and demonstrate a “grenz zone”, comprised of uninvolved dermis located between tumefaction and epidermis. Subcutaneous lesions are enveloped in a true capsule [4,5]. Enlarged, plexiform neurofibroma demonstrates multiple, tortuous, nerve fascicles designated as “bag of worms”. On cytological evaluation, miniature subgroups and clusters of spindle-shaped cells are loosely articulated. Tumor cells display minimal cytoplasm with uniform, elliptical or elongated nuclei and absent nucleoli. A neoplasm of minimal to moderate cellularity, haphazard dissemination of loosely configured, spindle-shaped cells with poorly defined cellular margins is delineated. The neoplasm is composed of interlacing fascicles of elongated cells incorporated with wavy, darkly-stained nuclei. Innumerable mast cells and stromal dissemination of collagen bundles of diverse magnitude with variable quantities of mucin is observed. Cellular component is intermixed within a myxoid to collagenous matrix. Encompassing coarse, collagen bundles are described as “shredded carrots” [4,5]. Cellular nuclei are miniature, hyperchromatic and wavy, recapitulating “diving dolphins”. Occasional nuclear enlargement and smudgy chromatin is observed. Tumor cells may be incorporated with monomorphic “buckled” or “comma-shaped nuclei”. Foci of divergent cellular differentiation can exceptionally appear such as occurrence of melanin pigmented cells. Focal or diffuse nuclear atypia is observed. Multinucleated giant cells are exceptional. Mitotic figures are minimal to absent [4,5]. Comprehensive proliferation of peripheral nerve elements is encountered. Schwann cells depict wavy, serpentine nuclei with pointed ends and are disseminated within wire-like collagen fibrils. Stroma is mucoid-rich with enmeshed mast cells. Wagner-Meissner corpuscles, pacinian corpuscles, fibroblasts and axons which can be emphasized with silver or acetylcholinesterase stain, neurofilament or neuron-specific enolase (NSE) are dispersed within the collagen [4,5]. Neurofibroma may

infiltrate encompassing soft tissue. An epithelioid morphology can be exhibited although skeletal muscle differentiation is infrequent. Verocay bodies, nuclear palisading or hyalinised thickening of vessels walls is absent [4,5]. Diffuse neurofibroma is a poorly defined, expansible, cellular proliferation circumscribing cutaneous adnexal structures and extending into subcutaneous tissue with adipose tissue infiltration. The neoplasm can entrap peripheral nerves or appear as an intraneural, diffuse neurofibroma. Characteristically, tumefaction displays pseudo-meissnerian corpuscles which are comprised of fibrillary or whorled Schwann cells [4,5]. Plexiform neurofibroma is constituted by multiple, entwined, hypertrophic nerve fascicles and classically demonstrates a serpentine pattern with multiple nodules. The variant denominates nodular, irregular expansion of nerve bundles and a prominent, enveloping myxoid matrix. Neoplasm is associated with neurofibromatosis type I. Tumefaction depicts perineurial cells enmeshed within a predominantly myxoid or oedematous stroma with intermingled, thick, collagen fibres. Tumor cells can display cellular atypia, nuclear enlargement or hyperchromasia, contingent to degenerative alterations [4,5]. Focal cutaneous neurofibroma and intraneural neurofibroma are also defined as pertinent subcategories. Frequently, localized subtype or infrequently, diffuse subtype demonstrate the following features.

- Enhanced cellularity in combination with or absence of atypia or elevated mitotic activity.
- Pigmented lesions associated with melanin production.
- Atypical or bizarre lesions with hyperchromatic, pleomorphic, atypical nuclei associated with degenerative alterations and a distinct, lamellar configuration.
- Epithelioid variant demonstrating cohesive nest of epithelioid tumor cells.

- Granular cell variant constituted of granular cells and eosinophils. Tumor recapitulates associated granular cell tumors.
- Lipomatous variant with diffusely disseminated adipocytes which are intrinsic to the neoplasm.
- Dendritic cell variant comprised of dendritic tumor cells with configuration of pseudo-rosettes.
- Hybrid Neurofibroma with intermingled schwannoma-like nodules discernible within a typical neurofibroma [4,5].

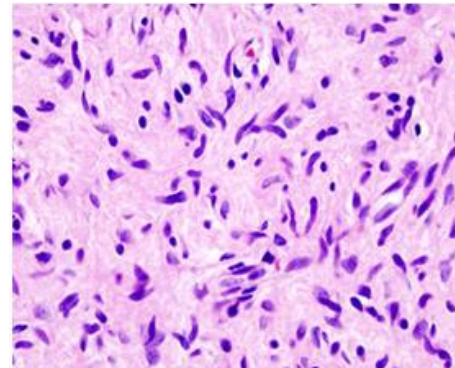


Figure 1: Neurofibroma enunciating aggregates of spindle-shaped cells and mast cells intermingled within a collagen-rich stroma and lack of cellular atypia.

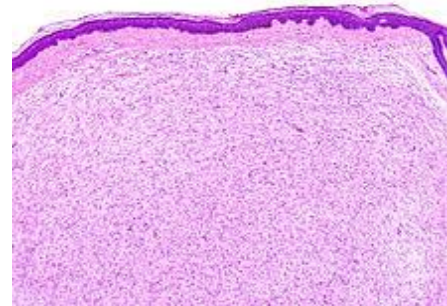


Figure 2: Neurofibroma demonstrating fascicles of spindle-shaped cells intermixed within a collagenous stroma and a superimposed epidermal layer.

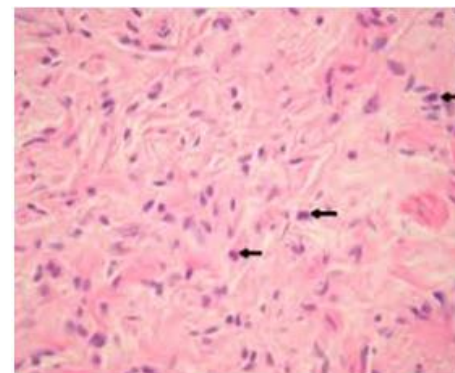


Figure 3: Neurofibroma exhibiting bundles of spindle-shaped cells dispersed within a collagenous stroma and an absence of atypia.

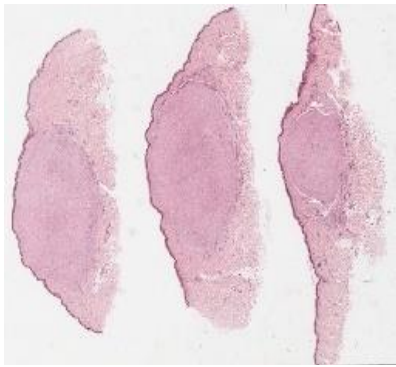


Figure 4: Neurofibroma delineating well circumscribed, encapsulated nodular aggregates with adjacent fibrous tissue

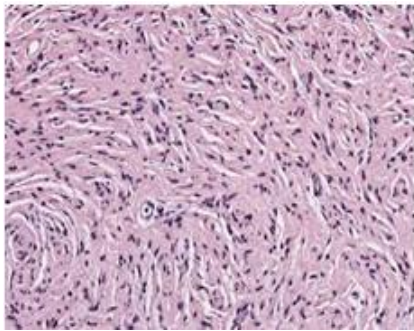


Figure 5: Neurofibroma depicting interlacing fascicles of spindle-shaped cells with dark, wavy nuclei and an encompassing collagenous stroma

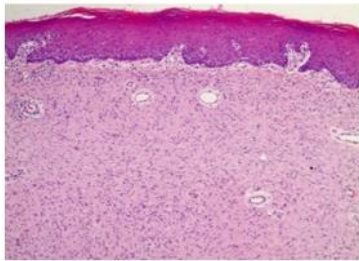


Figure 6: Neurofibroma enunciating bundles of spindle-shaped cells with wavy nuclei, absent mitosis and an enveloping collagen-rich stroma and a superimposed stratified squamous epithelium.

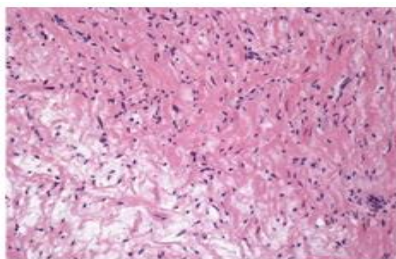


Figure 7: Neurofibroma comprised of fascicles of neuronal cells with wavy nuclei, mast cells and a circumscribing collagenous stroma.

On ultrastructural examination, Schwann cells exhibit an axonal envelop with plasmalemmal invaginations, thus configuring mesaxons [5].

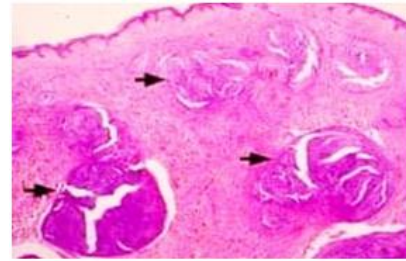


Figure 8: Neurofibroma composed of bundled of elongated cells with dark, wavy nuclei intermingled within a collagenous stroma.

Immune histochemical elucidation

Neurofibroma is intensely immune reactive to S100 protein, SOX10 and collagen type IV with fingerprint-like, immune reactive CD34. Immune reactivity to factor XIIIa can be beneficially adopted to differentiate neurofibroma from necrotized nevi. Tumefaction is focally immune reactive to calretinin and weakly immune reactive to epithelial membrane antigen (EMA) or podoplanin. Ki-67 proliferation index is minimal [1,2]. The neoplasm is immune reactive to myelin basic protein. An estimated 50% of tumor cells and Schwann cells are immune reactive to S100 protein. Spindle-shaped fibroblasts are immune reactive to CD34 with a distinct “fingerprint” pattern. Perineurial cells are occasionally immune reactive to epithelial membrane antigen (EMA). Intratumoural axons are immune reactive to neurofilament protein. Mucinous stroma is immune reactive to acid mucopolysaccharides. Staining with p16 can adequately demarcate atypical neurofibroma from low grade malignant peripheral nerve sheath tumor [1,2]. Excluding plexiform neurofibroma, the neoplasm is immune non reactive to epithelial membrane antigen (EMA). Also, cytokeratin, smooth muscle actin (SMA) and desmin are immune non reactive [1,2].

Differential diagnosis

Neurofibroma mandates segregation from:

Malignant peripheral nerve sheath tumor which is an aggressive, neurogenic neoplasm emerging from peripheral nerve or pre-existing nerve sheath tumor such

as neurofibroma. Approximately 50% neoplasms are concurrent with NF1 gene. Rapid tumor evolution in a preceding neurofibroma can indicate malignant metamorphosis. Morphologically, admixed foci of neurofibroma may be discerned. Malignant zones demonstrate enhanced cellularity, mitosis and necrosis. Tumor cells of malignant peripheral nerve sheath tumor demonstrate miniature, wavy nuclei and minimal nuclear hyperchromasia. Abundant, “shredded carrot” category of collagen dissemination is observed. Fascicular tumor configuration and mitotic figures are exceptional. Tumor necrosis is absent. The neoplasm is intensely immune reactive to S100 protein, collagen type IV, CD34, SOX10, moderately immune reactive to neurofilament and weakly immune reactive to podoplanin or epithelial membrane antigen (EMA) with minimal values of hyaluronan. Epithelioid variant of malignant peripheral nerve sheath tumor are immune reactive to INI1 (70%) [6,7].

Schwannoma is a benign, peripheral nerve sheath tumor comprised predominantly of Schwann cells. The neoplasm is associated with somatic and germline mutations of NF2 gene. The circumscribed, encapsulated, cellular neoplasm depicts Verocay bodies with alternating foci of hyper-cellular Antoni A and hypo-cellular Antoni B areas. Schwannoma commonly appears within 20 years to 50 years. Although sporadic, the neoplasm may emerge in concurrence with neurofibromatosis type 2 and exceptionally with neurofibromatosis type 1. Plexiform variant is infrequent [6,7]. The neoplasm is diffusely and uniformly immune reactive to S100 protein, intensely immune reactive to calretinin with scattered immune reactivity to CD34 and focal or absent immune reactivity to factor XIIIa. Malignant metamorphosis is extremely exceptional [6].

Perineuroma is an exceptional, benign, mesenchymal neoplasm engendered from perineurial cells, which lacks concurrence with neurofibromatosis. The neoplasm is

immune reactive to epithelial membrane antigen (EMA), Claudin-1, GLUT1, is variably immune reactive to CD34 and is immune non-reactive to S100 protein.

Dermatofibroma is a benign, neoplastic proliferation composed of fibroblasts and histiocytes. Tumefaction emerges as an indurated, dermal papule. The neoplasm is immune reactive to factor XIIIa (FXIIIa), CD163 or CD68 and is immune non-reactive to CD34 [6,7].

Dermatofibrosarcoma protuberans is a low grade, locally aggressive, fibroblastic sarcoma appearing within the dermis and subcutaneous tissue and is associated with COL1A1-PDGFB genomic fusion. Tumefaction demonstrates proportion of localized tumor recurrence at 50% with enhanced possibility of tumor progression and distant metastasis. The neoplasm is diffusely immune reactive to CD34 and immune non-reactive to S100 protein or factor XIIIa [6,7].

Palisaded encapsulated neuroma is a moderately cellular neoplasm. Epithelial membrane antigen (EMA) demonstrates a delicate, peripheral immune reactivity [6,7].

Superficial leiomyoma is a benign, dermal, smooth muscle neoplasm. It may emerge from the arrector pili muscle, thereby designated as pilo-leiomyoma. The neoplasm is immune reactive to smooth muscle actin (SMA), muscle specific actin (MSA) and desmin [6,7].

Neurotized melanocytic nevus is a benign nevus comprised of nests and aggregates of melanocytic cells disseminated within a loosely cohesive, neuron-laden stroma. Neurotized nevus is immune reactive to S100 protein although nevi are immune reactive to melanin A and immune non-reactive to factor XIIIa [6,7].

Ganglioneuroma is a benign neoplasm of neural crest origin, constituted by ganglion cells which arise from peripheral nerves. Tumefaction is commonly discerned

within the posterior mediastinum or retroperitoneum. Neoplastic Schwann cells are immune reactive to S100 protein and ganglion cells are immune reactive to synaptophysin.

Plexiform fibrohistiocytic tumour is an infiltrative, mesenchymal neoplasm composed of fibroblasts and histiocytes. The tumor commonly emerging upon the dermal-subcutaneous junction, is immune reactive to smooth muscle actin (SMA) and immune non-reactive to S100 protein [6,7].

Nerve sheath myxoma is a hypocellular neoplasm with an abundance of stromal mucopolysaccharides [7].

Desmoplastic melanoma is an invasive variant of malignant melanoma simulating a dermal scar and is frequently associated with malignant melanoma-in situ. Upon discernment, enlarged tumefaction demonstrates cytological atypia with occurrence of peripheral lymphoid aggregates [6,7]. Desmoplastic malignant melanoma is a neoplasm emerging with sun damaged cutaneous surfaces. The neoplasm commonly configures atypical, junctional, melanocytic hyperplasia or can emerge as melanoma- in situ. Tumor cells denominate elongated, hyperchromatic cells, a distinctive “packeted” pattern of tumor progression, foci of dense fibrosis and deep-seated, nodular lymphoid aggregates. The neoplasm is immune reactive to S100 protein and SOX10[6,7].

Tumefaction is immune non-reactive for melanocytic markers such as human melanoma black 45 (HMB45) antigen, melan A and tyrosinase. Exceptional, patchy immune reactivity to CD34 is observed.

Neurothekeoma is comprised of cellular, myxoid or mixed variants. Spindle-shaped or epithelioid tumour cells with abundant cytoplasm and indistinct cellular outline are admixed within a myxoid matrix with peripheral fibrosis. Nuclear atypia is variable and mitotic figures are frequent with atypical mitosis. The neoplasm

is immune reactive to vimentin, NKI/C3, CD10 and microphthalmia transcription factor (MITF) and is immune non-reactive to S100 protein and melanA [6,7].

Investigative assay

Solitary, superficial lesions can be adequately assessed with physical examination and/or obtainment of cogent tissue samples with subsequent microscopic examination. Enlarged lesions require tissue evaluation and/or assessment with computerized tomography (CT) or magnetic resonance imaging (MRI) in order to assess extent of lesion and optimal surgical strategy [8]. Upon computerized tomography (CT), a well defined, hypodense nodule with minimal or absent enhancement upon contrast administration is exhibited. Upon magnetic resonance imaging (MRI) tumefaction appears hypointense with T1 weighted imaging and hyper-intense upon T2 weighted imaging with heterogeneous contrast enhancement[7,8]. Upon MRI, superficial neurofibroma demonstrates homogenous or heterogeneous signal characteristics devoid of target. Adoption of whole body, hybrid positron emission tomography with magnetic resonance imaging (PET/MRI) in individuals with neurofibromatosis type I can be employed for discerning malignant transformation into malignant peripheral nerve sheath tumor. However, radiographic modalities may not suitably distinguish between neurofibroma and schwannoma [7,8].

Therapeutic options

Comprehensive surgical excision is a preferred treatment strategy and suitably alleviates the lesion. Localized tumor reoccurrence is extremely exceptional. Additional, alternative treatment options for managing cutaneous neurofibroma are absent. Instances with diffuse or plexiform neurofibroma, devoid of comprehensive surgical extermination, are subjected to total neoplastic resection for cosmetic or symptomatic relief. Adequate monitoring to assess rapid tumor evolution or reoccurrence can be adopted [7,8]. Sporadic lesions or

superficial lesions un-associated with neurofibromatosis type I can be subjected to marginal surgical excision. Deep-seated neurofibroma is managed conservatively. Occasionally, transection from parent nerve can be challenging, necessitating forfeiture of parent nerve in order to ensure comprehensive tumor resection [7,8]. Inherited neoplasms occurring in concurrence with neurofibromatosis type I require non-surgical therapy with preliminary discernment and risk stratification. Agent selumetinib is beneficially adopted in children. Plexiform neurofibroma is challenging to excise and incomplete resection is associated with frequent tumor relapse. Imatinib is employed for treating plexiform neurofibroma. Interferon-alpha is beneficial for progressive, symptomatic plexiform neurofibroma, unamenable to surgical resection[7,8]. Complications occurring with localized neurofibroma are contingent to surgical extermination with appearance of pain, hemorrhage, scarring and localized infection. Complications with plexiform neurofibromas are associated with intrinsic surgical procedures and are rarely due to inadequate eradication of the lesion. Neurofibromatosis 1 and persistent lesions are associated

with enhanced possible malignant metamorphosis with emergence of malignant peripheral nerve sheath tumor [7,8]. Neurofibroma is a benign neoplasm with extremely exceptional localized reoccurrence following comprehensive excision. Proportion of malignant metamorphosis is exceedingly minimal although malignant transformation occurs in approximately 10% instances associated with mutated NF1 gene [7,8]. Malignant metamorphosis into malignant peripheral nerve sheath tumor can emerge within deep-seated neurofibroma arising as a component of neurofibromatosis type I. Low grade malignant peripheral nerve sheath tumor is associated with diffuse nuclear atypia, enhanced cellularity and minimal mitotic activity. Nuclear atypia is denominated by nuclear enlargement (nuclear diameter exceeding ≥ 3 times normal nuclei of Schwann cells) and hyperchromatic nuclei [7,8]. Emergence of plexiform neurofibroma is indicative of neurofibromatosis 1 (NF1) disorder. Plexiform subtype is commonly associated with and appears as a precursor to malignant nerve sheath tumor. Subjects delineating multiple, localized neurofibromas mandate additional evaluation [7,8].

REFERENCES

1. Messersmith L, Krauland K (2020) Neurofibroma. Neurofibroma Stat Pearls Publishing, Treasure Island, Florida.
2. Hernandez MA, Duat RA (2016) Update on neurofibromatosis type I- not just café-au-lait spots, freckling and neurofibroma. An update. Part I dermatological clinical criterion diagnostic of the disease. *Actas Dermo-sifiliograficas* 107(6): 454-464.
3. Ferner RE, Gutmann DH (2013) Neurofibromatosis type 1 (NF1) - diagnosis and management. *Handbook of Clinical Neurology* 115: 939-955.
4. Schaefer IM, Fletcher CD (2015) Malignant peripheral nerve sheath tumor (MPNST) arising in diffuse-type neurofibroma- Clinico pathological characterization in a series of 9 cases. *The American Journal of Surgical Pathology* 39(9): 1234-1241.
5. Garozzo D (2019) Peripheral nerve tumors in neurofibromatosis 1- An overview on management and indications for surgical treatment in our experience. *Neurology India* 67(supplement): S38-S44.
6. Magro G (2018) Differential diagnosis of benign spindle cell lesions. *Surgical Pathology Clinics* 11(1): 91-121.
7. Harder A, Wesemann M, et al. (2012) Hybrid neurofibroma/schwannoma is overrepresented among schwannomatosis and neurofibromatosis patients. *The American Journal of Surgical Pathology* 36(5): 702-709.
8. Jokinen CH, Argyi ZB (2010) A typical neurofibroma of the skin and subcutaneous tissue: Clinicopathologic analysis of 11 cases. *Journal of Cutaneous Pathology* 37(1): 35-42.