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MPNST - A Diagnostic Dilemma

[1] Jagriti Gupta
[2] K K Gupta
[3] Rohit Jaiswal
[4] Himani Vashisht
[1] Sr. Lect., Dept. Of Oral Pathology & Microbiology
[2] Prof. & HOD, Dept. Of Periodontics & Implantology
[3] Reader, Dept. Of Oral Pathology & Microbiology
[4] PG Student, Dept. Of Periodontics & Implantology
Sardar Patel Post Graduate Institute Of Dental & Medical Sciences, Lucknow

Address For Correspondence:
Dr. Jagriti Gupta
3A, Vijay Nagar, Kanpur Road, Lucknow. (U.P.)
EmailID : jagritig26@gmail.com,
MobileNo : 09451975234
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Abstract
MPNSTs are rare malignant tumors of nerve sheath origin. It comprises of approximately 5-10% of all soft tissue sarcomas. The most preferred site of occurrence is lower extremities. Involvement of maxillo-mandibular area is extremely rare. It mainly affects individuals in the age range of 20-50 years. They can develop in pre-existing neurofibromas or schwannomas, de novo from peripheral nerves, or following radiation therapy. Most MPNSTs are easily diagnosed as malignant tumors, but the major challenge is faced in distinguishing them from fibrosarcoma, monophasic synovial sarcoma and leiomyosarcoma. These are difficult tumors to treat due to their inherently aggressive nature as well as limitations in both diagnostic and therapeutic methods.

Key Words
MPNST, neurofibrosarcoma, malignant schwannoma, triton tumor, Fluorodeoxyglucose positron emission tomography

Quick Response Code

Introduction

Malignant tumors arising from peripheral nerves or displaying differentiation along the lines of various elements of the nerve sheath like Schwann cell, perineural cell, fibroblast etc. are collectively referred to as malignant peripheral nerve sheath tumors (MPNSTs). The term malignant peripheral nerve sheath tumor (MPNST) is coined by WHO in the year 2002 to replace earlier terms, Malignant Schwannoma, Neurofibrosarcoma and Neurogenic sarcoma.

In 1935, Stout first interpreted this malignant growth as fibrosarcoma, though he revised his opinion in 1949, after observing the outgrowth of Schwann cells in vitro from such tumor. Stewart and Copeland, Vieta and Pack, and Das Gupta and Brasfield have contributed to an increased understanding of this tumor.[1]

MPNSTs are uncommon neoplasms originating from Schwann cells or nerve sheath cells. Most MPNSTs involve the proximal portions of the extremities. These are uncommon sarcomas that almost always arise in soft tissue. They can develop in pre-existing neurofibromas or schwannomas, de novo from peripheral nerves, or following radiation therapy. Comparatively few arise in the head and neck, a feature that contrasts with the distribution of benign schwannomas. Involvement of the maxillo-mandibular area is exceedingly rare.

MPNST is a rare malignant lesion and corresponds to malignant proliferation of any cell of nerve sheath like: schawnn cell, perineural fibroblast or endoneural fibroblast. A sarcoma is said to be MPNST if any one of three criteria is met:

- Tumor arises from peripheral nerve
- It arises preexisting benign nerve sheath tumor like neurofibromatosis(NF)
- Tumor displays constellation of histological features seen in foregoing situations and accepted as reflecting Schwann cell differentiation

MPNSTs histologically recapitulate the appearance of various cells of the nerve sheath. They range in appearance from tumors that resemble a neurofibroma to those resembling a fibrosarcoma.

Epidemiology

The tumour represents 10% of all soft tissue sarcomas and the incidence in head and neck region is only 8-20%.[2] Involvement of the maxillo-mandibular area is exceedingly rare.[3] It can occur either spontaneously or in association with Neurofibromatosis-1 (NF1). It is manifested mainly in association to NF1. Patients with NF1 develop sarcomas after a long latency period usually 10-20 yrs.

NF1, also known as "von Reckling hausen disease," is an autosomal dominant condition which is clinically characterized in part by pigmented skin lesions known as café-au-lait spots, benign cutaneous and subcutaneous tumors known as neurofibromas, distinctive bone lesions, and focal malformations of the iris. It is the most common single gene disorder in humans and results from the defective protein neurofibromin, which is thought to act as a tumor suppressor. Neurofibromatosis 2 (NF2), is characterized by tumors involving the cranial nerves, spinal nerves, and lesions of the brain and spinal cord. The defining feature of NF2 is bilateral acoustic neuromas, which are tumors affecting the auditory nerves, in turn causing hearing loss. The defective gene product in NF2 is known as merlin.

Etiology

MPNST may arise due to various factors, which include: -

- Germline mutation
- Therapeutic / occupational irradiation (10-20% of cases) with a latent period of more than 15 years
- "de novo" (i.e.from neuro-ectodermal tissue in sporadic cases)

Molecular and cytogenetic findings suggest that it is a multistep process. It shows thatgenes other than NF1 also participate in development of MPNST.NF1 have germline inactivation of NF1, in which both the alleles are inactivated. Progression of NF to MPNST is associated with number of additional chromosomal alterations.

Clinical Features

MPNST is a disease of adult life usually affecting individuals aged between 20-50 years. Children and elderly persons may also be affected rarely. Patients with NF1 syndrome develop MPNST approxi mately a decade before non syndrome patients. It shows equal predilection in males and females. MPNSTs are uncommon sarcomas that almost always arise in soft tissue. They are usually deep-seated and often involve the proximal upper and lower extremities as well as the trunk. The most preferred site for its occurrence is lower extremities, although a small percentage of lesions also occur in H&N region. MPNSTs arising from peripheral nerves may result in a variety of clinical patterns, including radicular pain, paresthesias and motor weakness. Most MPNSTs occur in conjunction with large peripheral nerves such as the sciatic nerve, the brachial plexus and the sacral plexus. The tumor can be noted as enlarging palpable mass several months before diagnosis. Pain is a variable complaint butis more prevalent in patients with NF1.Rapid enlargement occurs more often in the setting of NF1 and should raise concern for malignant degeneration of a neurofibroma. Dermal neurofibromas commonly encountered in cases of NF1have not been shown to undergo malignant transformation and do not usually require close monitoring. On the other hand, large nodular tumors associated with large peripheral nerves and deep extensive plexiform neurofibromas do not have the potential to undergo malignant transformation and should be observed diligently. Most common H&N area of involvement is neck and its occurrence in oral cavity is extremely rare.In soft tissues, the lesion usually appears with indistinct margins, may be ulcerated, painful or cause paresthesia. In the oral cavity, it may arise from tongue or soft palate. Other sites of involvement are lip, gingiva, palate and buccal mucosa. In rare cases, multiple MPNSTs can arise in the setting of NF1. Most of these tumors are considered high-grade sarcomas with the potential to recur as well as to metastasize.

The central tumors more commonly affect mandible and mandibular nerve as compared to maxilla. Primary intraosseous MPNST is rare and has been reported most frequently in the mandible.[4]

In the maxillofacial region, MPNST of jaws/soft tissues affect bone by 3 different mechanisms:

- When tumour tissue is localised extraosseously, it affects bone by secondarily eroding it
- It can develop within a nutrient canal primarily and involving bone secondarily
- It can primarily arise within central medullary canal

Radiographically, it appears as well-delineated tumour. It may present as lytic lesion with sharp sclerotic or partially sclerotic margins with occasionally disruption of osseous cortex. It can be multilocular showing diffuse radiolucency. The tumor originating from mandibular nerve appears as smooth radiolucency.

On CT, MPNSTs present as hypodense, non-homogenous masses due to areas of degeneration and areas of varying cellular density.[5] Magnetic resonance imaging (MRI) is the imaging modality of choice. Under MRI, it exhibits isointense signal intensity on T1-weighted MRI images and hyperintensity on T2 –weighted images. Large tumors, invasion of fat planes, heterogeneity, ill-defined margins and edema surrounding the lesion are more suggestive of MPNSTs.

Staging

Staging describes the tumor characteristics and in turn facilitates proper planning and adequate treatment. It also offers prognostic information. With regard to soft tissue sarcomas, staging is dependent on histological grade, tumor size, tumor depth and presence or absence of metastasis. The staging is based upon imaging studies, which demonstrate the local and distant metastasis and also on the histologic grade, which describes the histological characteristics of individual tumor cells. A number of staging system has been described. The most commonly employed staging system is American Joint Committee on Cancer (AJCC) staging system for soft tissue sarcomas.[6] Stage I essentially describes any low grade small soft tissue sarcoma without evidence of metastasis. Stage II describes small high-grade tumors and large but superficial high grade tumors but without distant metastasis. Stage III describes high-grade large tumors which are deep. Stage IV includes any tumors with evidence of metastasis. One limitation of this staging system is that it does not reflect the tumor's anatomic location.

A biopsy is an integral part of the staging system. It offers both a histologic tissue diagnosis and the ability to determine the grade of the lesion. This information, in turn, permits adequate planning and adjuvant treatment such as radiation or chemotherapy. In addition, this information is incorporated into the tumor staging process which provides prognostic information with regard to the disease and treatment generalizations.

Fine needle aspirations or FNAs is a biopsy method employed to obtain individual cells for cytologic review. It can be done with a very small needle which is more easily tolerated by the patient and is often useful to establish the presence of malignant cells. However, it is not large enough to demonstrate the architectural pattern within a tumor and for this reason is not often used to make an initial diagnosis. In cases of established diagnoses, such as after surgical resection of a tumor, FNA can often be successfully used to sample tissue which is suspected to be recurrent disease.

A second type of biopsy is a core needle or tru-cut needle biopsy, which uses a larger hollow-bored needle gauge to obtain a more substantial tissue sample. This type of sample offers inspection of both individual cells as well as the architectural arrangement of those cells within a given part of the tumor mass. This information is often important in establishing a histopathologic diagnosis. In many tertiary care cancer centers, core needle biopsies are often performed with either CT or ultrasound image guidance. This is an outpatient procedure and it allows for adequate tissue sampling while minimizing bleeding and minimizing contamination or seeding of surround tissue with tumor cells. In addition, it often avoids the need for general anesthesia. In some cases a formal open biopsy is required. This can either be an incisional biopsy, where a small piece of tissue is removed from the larger tumor mass, or an excisional biopsy, in which case the entire tumor is removed. In general, an incisional biopsy is recommended when a sarcoma is suspected.

Macroscopy

Macroscopic appearance of tumor is of a large, fleshy, opaque, white-tan mass, whose surface is usually marked by areas of secondary hemorrhage and necrosis.It may also present as large, fusiform/eccentric mass in major nerve.

Thickening of nerve proximally and distally to main mass indicates spread of neoplasm along epineurium and perineurium.

Histological Features

MPNSTs recapitulate the appearance of various cells of the nerve sheath. They range in appearance from tumors that resemble a neurofibroma to those resembling a fibrosarcoma.[6] Most MPNSTs resemble fibrosarcomas. The cells recapitulate features of normal Schwann cell. Nuclei appear wavy, buckled/comma shaped. Cytoplasm is lightly stained and usually indistinct. Cells can range from spindled or fusiform to round in shape, arranged in sweeping fascicles.Densely cellular fascicles alternate with hypocellular myxoid zoneswhich swirl and interdigitate with one anothergiving a marble-like effect. It also exhibits peculiar nodular/whorled arrangement of spindled cellswith nuclear palisading present focally. Cellular and nuclear pleomorphism may be quiet pronounced and mitotic activity is usually high.[7] Several other features quiet characteristic of MPNST are-

- hyaline bands and nodules
- extensive perineural & intraneural spread of tumor
- proliferation of tumor in subendothelial zones of vessels
- neoplastic cells appear to herniate into lumen
- Histologically, MPNST- classified into 3 categories
- Epithelioid
- Mesenchymal
- Glandular

Epitheliod variant demonstrates plump, rounded or ovoid epitheliod cells scattered throughout the lesional cells. These cellshave vesiculated or hyperchromatic nuclei.

MPNST may sometimes show rhabdomyoblastic differentiation which is termed as Triton tumor.[8] The spindle cells are interspersed having large, plump, rounded or strap cells with eosinophilic fibrillar cytoplasm and cross striations.

Glandular MPNST exhibits areas of well differentiated ductal structure lined by simple stratified, cuboidal or columnar epithelial cells with occasional goblet ells. Lumina contains PAS-positive, diastase resistant mucous.Rare MPNST may contain multiple sarcomatous tissues like osteosarcoma, chondrosarcoma and angiosarcoma.

Differential Diagnosis

Most MPNSTs are easily diagnosed as malignant tumors, but the major challenge is faced in distinguishing them from fibrosarcoma, monophasic synovial sarcoma and leiomyosarcoma. Fibrosarcoma and Synovial sarcoma have more uniform fascicular pattern,contain symmetric fusiform cells resembling fibroblastsand lack features of neural differentiation.Monophasic synovial sarcoma contains densely hyalinized or calcified areas (or both) with areas rudimentary epithelial differentiation in the formsof clusters of round cells with clear cytoplasm. Leiomyosarcoma is easily distinguished, as the cells have deeply eosinophilic cytoplasm, centrally placed blunt ended nuclei and juxta nuclear vacuoles.

Diagnosis of malignancy depends on-

- enhanced cellularity
- diffuse atypia
- low level of mitotic activity

Diagnosis

The diagnosis can be done by observing a constellation of histological features exhibited by MPNST. IHC can be utilized in identifying nerve sheath differentiation. The most commonimmunohistochemical markers described inthe literature include: S-100, CD34 and EMA.[9] S-100, which is traditionally regarded as the best marker for MPNST, has limited diagnostic utility and is positive in only about 50-90% of the tumors. In high grade MPNST, only scattered, if any, tumor cells are S-100 positive. On the other hand, although sensitive, CD56 and PGP 9.5 expression is in no way specific for tumors of MPNST. Thereby, MPNSTs per se lack sufficiently specific and sensitive immunohistochemical marker. Recent studies suggest that nestin, which is an intermediate filament protein, is more sensitive for MPNST than other neural markers (S-100, CD56 and PGP 9.5) and immunostains for nestin in combination with other markers could be useful in the diagnosis of MPNST.[10]

Fluorodeoxyglucose positron emission tomography (FDG PET) is a dynamic imaging modality which evaluates metabolic activity by quantitatively assessing intracellular glucose use. It has been shown to reliably identify areas of increased metabolic activity such as those seen in malignancies.

Therapeutic Modalities

The treatment of MPNST consists primarily of radical surgical excision, possibly along with adjuvant radiation therapy and chemotherapy.[11]

Surgical Therapy

The mainstay of treatment is surgical resection. The goal of the operation is to achieve complete surgical excision of the tumor with negative (wide) margins. This offers the best outcome with respect to both local recurrence and distant metastases.

Radiation Therapy

Radiation therapy has become an integral part of local disease control in most soft tissue sarcomas and likewise can be employed in pre-operative, intraoperative, and post-operative settings for MPNST. Treatment of soft-tissue sarcomas with adjuvant radiation therapy has yielded a statistically significant reduction in the rates of local disease recurrence. It has not, however, had a meaningful reduction in either rates of distant metastases or overall survival.

Preoperative external beam radiation therapy is administered before surgical resection. This approach offers a number of potential benefits including accurate radiation planning and tumor localization, smaller treatment volumes, and smaller dose requirements. Pre-operative treatment also offers the theoretical advantages of the "oxygen-enhancement effect" which argues that radiation treatment is more effective in the setting of well-oxygenated tissue. Finally, radiation therapy may result in substantial tumor necrosis, making tumor spill less likely and in some instances making successful limb salvage technically easier. These benefits come at a cost of delayed wound healing, surgical delay following radiation treatments, and less tissue from which to obtain a diagnosis. In such cases a postoperative boost dose of irradiation is administered for positive margins.

Post-operative radiation therapy is administered following surgical resection. Post-operative radiation therapy offers the patient immediate surgical excision, fewer wound healing complications, and a larger specimen from which to make a tissue diagnosis. Its disadvantages, however, are larger treatment volumes, higher dose requirements, and the risk of seeding the surgical scar and bed with viable tumor.

When it is anticipated that a close or microscopically positive margin will occur at the time of resection, intraoperative radiation therapy may be administered in the operating room immediately following surgical resection. Similarly, radiation administered via catheters (plastic tubes) which, are implanted in the surgical bed at the time of resection and loaded with radioactive material in the peri-operative period is another option that may be considered to help with a close or positive margin. This type of radiation is referred to as brachytherapy. Both methods offer focal concentrated treatment, limited collateral damage to surrounding tissue, smaller overall doses, and minimal to no delay in treatment following resection. However, these treatment methods are employed without knowing final pathology margin results. They may also result in wound healing problems.

Chemotherapy

Chemotherapyis intended for systemic disease which is either too small to detect or too diffuse, rendering local treatment techniques ineffective. The use of chemotherapy is only employed in high-grade disease, in which metastatic disease is likely. The benefits of chemotherapy must be weighed against its side-effects, some of which are irreversible. For this reason, the decision to treat with chemotherapy is somewhat tailored to an individual patient and his or her individual disease.

Chemotherapy can be administered in the pre-operative and post-operative settings. Benefits of pre-operative chemotherapy include immediate treatment of micrometastatic disease and the potential for tumor shrinkage in certain chemotherapy-sensitive tumor types. It has also been shown to radiosensitize some tumors, making a combined protocol of radiation therapy and chemotherapy synergistic. Chemotherapy is typically not administered in the case of smaller lesions, defined as less than 5 to 8 cm in maximum dimension. It is often avoided in cases which are confined to local cutaneous or subcutaneous locations. Significant medical co morbidities often preclude chemotherapy treatment. Large, deep, high grade tumors and tumors which demonstrate metastases or metastatic potential are typical indications for chemotherapy treatment.

Recurrence and distant metastasis

Most MPNSTs are high-grade sarcomas due to its local recurrence and distant metastasis. Patients with NF are at greatest risk for developing sarcomas, including MPNST. The incidence of MPNST arising in NF is 4.6%, which is much higher than the 0.001% in general population. The most common metastatic site of MPNST is the lung.[12] Metastasis can occur through hematogenous routeand most common metastatic site for MPNST islung, bone and pleura. It occurs in a more aggressive fashion in patients with NF1. Thetransformation rate of NF1 to MPNST is approximately 5% with an overall, 5-year survival of 40-75%.

Prognosis

In the context of soft tissue sarcomas in general, tumor grade is recognized as having the greatest prognostic impact. The prognosis of MPNST depends on size, stage and grade of the lesion. It is also determined by status of surgical margins, necrosis and use of adjuvant radiation during therapy. In addition, large tumor size, deep tumor location, and positive surgical margins have also been cited as poor prognostic factors. There has been some evidence that poor prognosis is also reflected by an increased proliferation index of Ki-67 as measured by immunohistochemical analysis. Ki-67 is an antigen which can be used to quantify the fraction of cells undergoing division.

Conclusion

MPNSTs are difficult tumors to treat due to their inherently aggressive nature as well as limitations in both diagnostic and therapeutic methods. To date, advances in imaging methods such as MRI and PET have realized earlier disease detection and characterization. Advancement of immunohistochemical analysis has facilitated more accurate disease identification and classification.Treatment of sarcomas requires considerable multidisciplinary approach to the benefit of the patient.Future gains for treatment modality will depend upon proper understanding of genetic alterations and molecular biology of soft tissue sarcomas.

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