Melanotic Neuroectodermal Tumour of Infancy

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Introduction

Melanotic Neuroectodermal Tumour of Infancy (MNTI) is an uncommon neoplasm found predominantly in infants, with around 220 cases reported so far in world literature. 92% of the reported cases have been found in children less than one year of age and 82% of cases have been within the first 6 months of infancy [1,2,3]. This tumour has a predilection for the craniofacial region and is most frequently found in the maxilla (72%) followed by cranial vault (12%), mandible (5%) and brain (4%) [4,5]. The remainder of the sites where the lesion has been reported are epididymis, mediastinum, ovaries and few isolated cases in the thigh, foot, scapula, cheek and zygoma.

The earlier uncertainty on the origin of the tumour resulted in a variety of terms [6,7] for the lesion. Krompecher (1918) who first reported this neoplasm referred to it as congenital melanocarcinoma. The other names proposed have been melanotic progonoma, pigmented ameloblastoma, retinal anlage tumour, melanotic epithelial odontoma, and pigmented congenital epulis [8]. Borello and Gorlin in 1966 referred to the tumour as melanotic neuroectodermal tumour of infancy and suggested neural crest origin on the basis of high excretion of vanillyl mandelic acid [9] by the patients which is characteristic of tumours of neural crest origin, namely pheochromocytoma, neuroblastoma and ganglioneuroblastoma [10,11]. The neural crest origin has further been established from the support received on the basis of immunohistochemical, ultrastructural and biochemical analysis.

MNTI is a locally aggressive benign lesion with a recurrence rate of 15%. About 16 cases of malignant variants (6-7%) reported, have been from CNS.

Keeping in mind the locally aggressive behaviour of this neoplasm, its tendency for recurrence and the highly proliferative nature of its constituent cells, the management proposed for this lesion is early surgery in the form of either enucleation with aggressive curettage or en bloc resection, depending upon the extent,

proximity of the lesion to vital anatomic structures and the histopathological report.

Case Report

A 5 month old male infant was referred to the oral and maxillofacial clinic of Department of Dental Surgery with a rapidly growing swelling in the maxilla. The parents of the child noticed a small protuberance on the right side of the upper jaw when the child was 3 months old, which kept on growing in dimension and had lately started interfering in suckling.

Examination revealed a diffuse midfacial swelling face with obliteration of the nasolabial fold, elevation of upper lip and ala of nose on the involved side, and extending superiorly to the infraorbital margin. Intraorally, a bluish-tinged swelling with firm submucosa was noticed involving the maxilla extending posteriorly upto the second deciduous molar area, obliterating the mucogingival sulcus (Fig-1).

Radiographs revealed an expansile destructive bony lesion with irregular margins involving the maxilla, containing deciduous central incisor of that side which was displaced and presented a floating appearance within the osteolytic area.

Aspiration biopsy of the lesion did not reveal anything, however an incisional biopsy specimen under light microscope showed two components of tumour cells - large epitheloid somewhat eosinophilic cells containing variable amount of melanin, the melanocytic cells and a second population of small, basophilic neuroblastic cells. The cells were arranged in lobules set in a desmoplastic stroma (Fig-2).

En bloc resection of the tumour was accomplished. The anterolateral wall and floor of the maxillary antrum were found to be intact. Small grey-black patches were noticed in the surrounding bone, which were thoroughly curetted and cauterised with Carnoy's solution. The excised specimen was a 4x2x1.3 cm large, opaque, greyish mass of tissue having irregular black areas, with the crown of the deciduous central incisor projecting from its surface and some peripheral bone spicules. The specimen exhibited resistance when cut, revealing an irregular grey surface with numerous pin point foci of blackish discoloration on cut section. Histological examination of both specimen revealed alveoli-like spaces lined by epitheloid cells containing brownish black pigment and several clumps of small dark cells re-

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Fig. 1 : Intraoral tumour mass causing expansion of buccal/labial as well as palatal cortical plates extending upto deciduous molar region

Fig. 2 : Low power view of tumour shows "biphasic" pattern of pigmented epithelial cells forming tubules and clusters of small round cells of neural origin. HE 10X

Fig. 3 : Melanosomes taking up silver stain in the epithelial component of the tumour. Primordial dental anlage seen in the lower part. Masson Fontana 4X

sembling neuroblasts, set in a fibrous stroma (Fig-2). The intracellular granular pigment in the epitheloid cells was confirmed to be melanin by the Masson-Fontana Stain (Fig-3). An area of dental anlage lined by columnar cells was

Fig. 4 : Electron microscopic view of the epitheloid cells showing electron-dense melanin granules and melanosomes and premelanosomes in varying stages of differentiation. 8000X

Fig. 5 : Immunohistochemical stain for PCNA shows nuclear localisation in the large cells of the stain pigment. 40X

also seen. Electron microscopic study revealed a 'biphasic'-cell population consisting of :

a) small darkly staining neuroblastic cells, containing secretory granules, hyperchromatic nuclei and irregular fibrillar cytoplasmic processes resembling neurofilaments.

b) large epitheloid cells containing melanosomes (Fig-4).

The specimen were also subjected to immunohistochemical analysis and expression of Proliferating Nuclear Cell Antigen (PCNA) was tested. 40 to 50% of tumour cells exhibited PCNA positivity confirming the highly proliferative nature of these cells (Fig-5).

Discussion

MNTI is a rare, benign but locally aggressive neoplasm found in children of less than one year of age. The tumour is frequently found in craniofacial region with predominance of anterior maxilla, followed by

the skull, mandible and brain and a few cases reported from other parts of the body.

Clinically, it is a fast growing, non ulcerative swelling, with or without pigmentation in the overlying soft tissue. In the maxilla, the tumour displaces the lip and appears as a dark swelling. It needs to be differentiated from other maxillary swellings i.e. odontogenic cysts, eruption cysts, odontogenic tumours, haemangioma, lymphangioma, neuroblastoma, histiocytosis-X and osteogenic sarcoma. Radiographically, the picture shows central area of radiolucency with poorly demarcated borders or multilocular appearance. Teeth in the lesion appear to be floating within the radiolucent area because of displacement from normal anatomical and development site. The radiographic picture makes it mandatory to differentiate this tumour from malignancy.

Different histogenetic theories like the congenital, retinal anlage and odontogenic origin of this tumour were proposed earlier. However, immunohistochemical analysis, biochemical and ultrastructural studies have supported the theory of neural crest origin of this lesion. High urinary excretion of vanillylmandelic acid, presence of biphasic cell structure resembling melanocytes and neuroblasts and immunohistochemistry are all in favour of neural crest origin of this lesion. In ultrastructural studies [12] Nelson and Newman (1995) showed that the small darkly staining cells stained positively for Neuron Specific Enolase (NSE) and Synaptophysin, indicating them to be neuroblasts and large epitheloid cells comprising the second cell population stained positively with the antibodies HMB-45 and NKI-Beteb, which are melanocytic markers, confirming them to be melanocytes.

Evaluation of immunohistochemical expression of several cell cycle proteins (P53, MDM-2, Cyclin D1, Cyclin A and PCNA) has been carried out by D'Souza and Merly [13]. The large melanin containing epitheloid cells stained positive for Cyclin D1, Cyclin A, PCNA and MDM-2, suggesting that these cells constitute the proliferative elements of MNTI. MDM-2 expression is also important for the tumour's biological behaviour and development because being a proto-oncogene, it interacts with P53 protein inhibiting its regulatory function. The tumour cells seen under light and electron microscope in our cases showed a biphasic/dual cell morphology with islands comprising large epitheloid cells containing varying amounts of melanin and a more central population of neuroblast-like cells which are arranged in lobules, set in a desmoplastic stroma. The small basophilic cells grouped in alveolous-like structures stained positively for NSE

[14], whereas the larger cells stained positively for keratin, vimentin and NSE. Only S-100 protein did not stain any of the cell types of the MNTI. Further, on immunohistochemical analysis, the tumour cells particularly the melanocytic cells rather than the neuroblastic ones, were found to exhibit a high PCNA positivity (40-50%) confirming their highly proliferative nature.

The treatment modality proposed for the eradication of this lesion is surgical enbloc resection or enucleation and aggressive curettage.

The extension of the lesion in our case was observed even beyond the resected margins warranting extended resection and aggressive curettage. It is important to institute the proper surgical protocol as soon as possible keeping in mind the locally aggressive behaviour of this neoplasm, its recurrence and malignant transformation and the highly proliferative nature of its constituent cells. Follow-up of these patients is mandatory to rule out any recurrence.

MNTI is an aggressive, rare pigmented neoplasm seen almost exclusively in infants with a predilection for the craniofacial skeleton, particularly the maxilla. One may seldom come across this lesion in a lifetime. It is a tumour of neural crest origin and is derived from two distinct but related cell lines. Histogenetic and immunohistochemical studies have shown that it is the epitheloid melanocytic cells rather than neuroblastic ones which constitute the proliferative element of this neoplasm. Early surgery in the form of enbloc resection or enucleation with aggressive curettage is the treatment of choice to limit the amount of tissue destruction by tumour growth and to reduce the risk of recurrence and possible malignant transformation.

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RADIOLOGICAL QUIZ

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A 45 year old male, known hypertensive presented with complaints of acute onset retrosternal non-radiating chest pain. ECG showed left axis deviation. Plain

X-ray chest (Fig-1) followed by contrast enhanced CT chest was done (Fig-2).

Fig. 1 : Plain radiograph chest PA view

Fig. 2 : Contrast enhanced CT chest section in soft tissue window

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