

Melanotic neuroectodermal tumor of infancy: a case report

Tumor neuroectodérmico melanocítico de la infancia: reporte de caso

CLAUDIA PATRICIA PEÑA VEGA¹, LIZETH VANESSA FAJARDO ORTIZ², ERIKA ALEXANDRA PARRA SANABRIA³,
EDNA MARGARITA QUINTERO CANASTO⁴, HUMBERTO QUINTANA MUÑOZ⁵

- ¹ M.Ed., Universidad Pedagógica Nacional. Oral Pathologist, Pontificia Universidad Javeriana. DDS, Pontificia Universidad Javeriana. Oral and Maxillofacial Surgeon, Universidad Nacional de Colombia. Pediatric Maxillofacial Surgery, University of Pennsylvania. Associate Professor, Universidad Nacional de Colombia School of Dentistry. Head of the Department of Oral Health. ORCID: 0000-0002-4532-3642
- ² DDS, Universidad Nacional de Colombia. Bogotá, Colombia. ORCID: 0000-0002-4367-9928
- ³ DDS, Universidad Nacional de Colombia. Bogotá, Colombia. ORCID: 0000-0002-3158-8826
- ⁴ M.D., Universidad de Cartagena, Hospital de la Misericordia. Clinical and Anatomical Pathologist, Universidad Nacional de Colombia. Fellowship in hematopathology, Universidad de Barcelona. Pathologist, Universidad Nacional de Colombia School of Dentistry. ORCID: 0000-0003-1776-0711
- ⁵ Pathologist, Universidad Nacional de Colombia School of Dentistry. ORCID: 0000-0001-7707-6781

Abstract

Melanotic Neuroectodermal Tumor of Infancy (MNTI) is a rare neoplasm originating from neural crest cells, which generally affects pediatric patients, most frequently during the first year of life. The behavior of MNTIs is benign, locally aggressive, with a recurrence of 10-15% and eventually malignant in 6.97%. This study describes the clinical, imaging, histopathological, immunohistochemical characteristics and the management of MNTI in a 5-month-old girl, whose lesion was resected and monitored. The present case illustrates the benefits of multidisciplinary integration for a correct diagnosis to ensure adequate therapeutic management, in addition to providing a report on this rare and understudied pathology.

Keywords:

melanotic neuroectodermal tumor, infancy, pathology, maxillary

Resumen

El Tumor Neuroectodérmico Melanocítico de la Infancia (TNEMI) es una neoplasia infrecuente derivada de las células de la cresta neural, que afecta generalmente a pacientes pediátricos y se presenta con mayor frecuencia durante el primer año de vida. Su comportamiento es benigno, localmente agresivo, con una recurrencia de 10% a 15% y eventualmente maligno en un 6.97%. En este estudio se describen las características clínicas, imagenológicas, histopatológicas, inmunohistoquímicas y el manejo del TNEMI en una niña de 5 meses de edad, a la cual se le realizó resección de la lesión y seguimiento. El presente caso ilustra el beneficio de la integralidad multidisciplinaria que permite establecer un diagnóstico correcto para asegurar un manejo terapéutico adecuado, además de aportar un reporte sobre esta patología poco frecuente y estudiada.

Palabras clave:

tumor neuroectodérmico melanocítico, infancia, patología, maxilar

Submitted: January 23/2019 – Accepted: August 9/2019



How to quote this article: Peña-Vega CP, Fajardo-Ortiz LV, Parra-Sanabria EA, Quintero-Canasto EM, Quintana-Muñoz H. Melanotic Neuroectodermal Tumor of Infancy: a case report. Rev Fac Odontol Univ Antioq. 2020; 32(1): 104-112. DOI: <http://dx.doi.org/10.17533/udea.rfo.v32n1a10>

INTRODUCTION

Melanotic Neuroectodermal Tumor of Infancy (MNTI) is a rare, pigmented neoplasm that originates at the neural crest. The World Health Organization (WHO) has identified it as a benign congenital head and neck abnormality,^{1,2} with expansive and locally aggressive growth, although a few cases with potential malignant transformation have been reported.^{2,3} It occurs mainly during the first year of life⁴⁻⁶ as a mass affecting the maxilla; however, it has been described in the mandible, head, neck, brain, epididymis, mediastinum, shoulder, scapula, anterior fontanelle, femur, uterus, and ovary.^{2,3,7-8}

This tumor has been referred to with a variety of names, including congenital melanocarcinoma, retinal anlage tumor, pigmented congenital epulis, melanotic progonoma, retinal choristoma,^{7,9} pigmented adamantinoma, melanocytic epithelial odontoma, melanocytic ameloblastoma, melano-ameloblastoma¹⁰ and melanocytoma.¹¹

The morphological expression of MNTI is similar to small round cell tumors, so it is necessary to conduct differential diagnosis, including Ewing's sarcoma/PNET, Embryonic Rhabdomyosarcoma, Lymphoblastic Lymphoma,^{8,11} Small Cell Desmoplastic Tumor, Mesenchymal Chondrosarcoma, and Neuroblastoma¹⁰ (Table 1).

Table 1. Differential diagnostic characteristics

Features	Ewing's sarcoma/PNET	Embryonic Rhabdomyosarcoma	Lymphoblastic Lymphoma	Small Cell Desmoplastic Tumor	Mesenchymal Chondrosarcoma	Neuroblastoma
Location	Femur, tibia, humerus	Soft tissues, orbit, nasopharynx, oral cavity	Distal femur	Intra-abdominal	Craniofacial (mandible)	Retroperitoneal (Suprarenal marrow. Zuckerkindl organ)
Age	Under 20	Under 15 years. Half under 5 years	Over 30 years	Young patients	20-30 years	18-21 months
Sex	M: F: 1.4:1	M: F: 1.5:1	Same	Higher in men	Same	Higher in men
Clinical	Pain/mass. Constitutional Symptoms	Infiltrating mass	Soft tissue mass	Intra-abdominal mass	Pain and edema	Mass, fever, anemia, diarrhea, increased urinary catecholamines
Rx	Onion bulb-like image	Radiodense mass with poorly defined edges	Soft tissue mass and bone rarefaction	Solid intra-abdominal mass	Lithic and sclerotic image	Mass with calcification
Macroscopy	Dark grey	Non-circumscribed fleshy mass	Fishmeal mass	Grey mass and satellite nodules	Firm to soft mass	Yellow nodular or multilobular mass
Microscopy	Round, small, blue cell	Primitive cell	Multilobed, indented cell (Chicken cell lymphoma)	Small cell nests separated by desmoplasia	Round, small, blue cell. Cartilage and hemangioperitoid vessels	Small round cell nests (Homer-Wright rosettes) and fibrillary matrix
Immunohistochemistry	CD99, FL11, CK	MyoD1, Myogenin	CD45, TDT, CD43, CD79A	WT1, CK, NSE, Desmin	CD99, SOX9, PS100, ERG, FL1 (-)	NB84, NSE, Chromogranin, Synaptophysin, CD56
Molecular pathology	EWSR1-ETS (Fusion)	Chromosomal gains (2, 8, 11, 12, 13, 20)	EWSR1 T-cell receptor gene	EWSR1-WT1 Fusion	HEY1-NCOA2 fusion	Amplified MYCN
Treatment	Multimodal	Surgical, multimodal, and radiation therapy	Chemotherapy and radiation therapy	Surgical and Multimodal	Surgical	Surgical and Multimodal
Prognosis	Survival 65% to 5 years	Survival 92% to 5 years	Survival 95% to 5 years	Poor survival	Very aggressive	Depends on the degree of differentiation

Source: by the authors

The purpose of this report is to describe a new case of MNTI including a literature review. Since this is a rare pathology, it becomes necessary to report its clinical and radiographic characteristics, and especially the histopathological ones supported by immunohistochemistry techniques, providing clinicians with guidelines and tools to issue a comprehensive diagnosis and thus perform the corresponding treatment.

CASE DESCRIPTION

A 5-months-old female patient was referred to the Oral and Maxillofacial Surgery Service of the Hospital La Misericordia Foundation

(HOMI) as she had a clinical condition of one month of evolution consisting of a progressively growing tumefaction in the upper lip and gum, limiting food intake because of pain, as well as mechanical difficulty for suction.

The physical examination showed a deformed contour with elevated alar base, deletion of left nasogenian sulcus, abnormal nose shape due to increased size, upper proquelia, and violet epidermis; intraorally, it had a pigmented and expansive fixed indurated mass measuring approximately 2.0 cm at the level of the alveolar ridge of teeth 61, 62 and 63, with defined edges compromising the vestibular floor (Figures 1A and 1B).

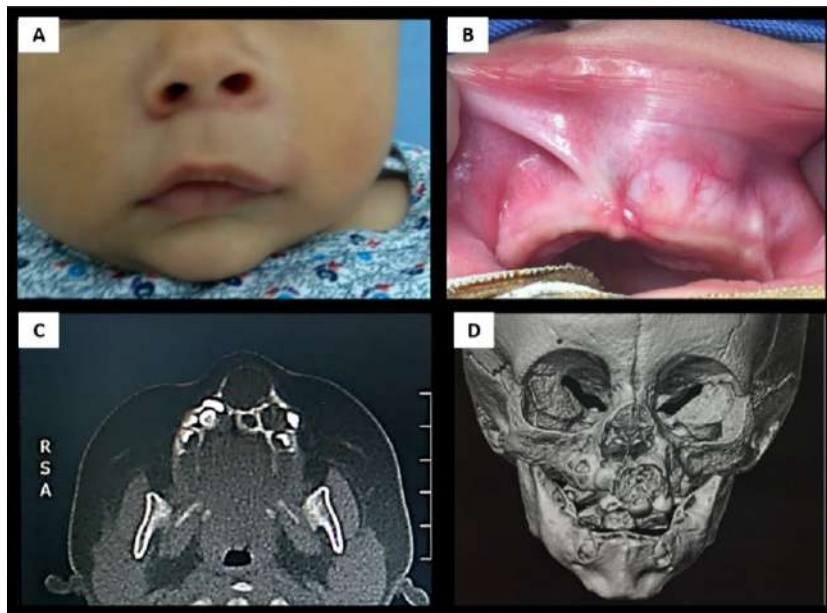


Figure 1. Melanotic Neuroectodermal Tumor of Infancy. A). Altered contour due to indurated mass at the alar base and deformed left nose, upper proquelia, and violet epidermis. B). Deformed contour on anterior alveolar maxillary region with pigmented, bluish mass. C). TAC axial cut: defined, multilocular, expansive maxillary lytic lesion. D). Tomography, 3D reconstruction: lesion with isodense content compromising premaxilla and left maxillary portion expanding to floor of nostrils. Lesion dimension: 27.4 mm x 13.7 mm x 17.6 mm (HOMI Case)

Source: by the authors

Computed Tomography (CT) was conducted with three-dimensional reconstruction, showing a multilocular, defined and expansive intraosseal lesion of isodense content measuring 27.4 mm x 13.7 mm x 17.6 mm (Figures 1C and 1D), partially obstructing the lower ipsilateral meatus with concomitant of left lateral nasal slope.

Upon informed consent, the tumor was removed under general anesthesia, using marginal resection and germenectomy of 61, 62 and 63. The HOMI Pathology Service received a surgical specimen with five lobed fragments of different size, the largest being 1.5 cm in diameter, violet, bluish and semi-soft, and three temporary teeth corresponding to 61, 62 and 63. The histopathological study showed a fibrous stroma lesion, with

cell pattern arranged in alveoli and nests. The alveoli were peripherally surrounded by large cells loaded with melanin pigment and centrally occupied by groups of small neuroblastic cells, which are also grouped into stromal nests with isolated expression of cell crushing (the Azzopardi effect, due to fall of DNA from nucleus) (Figures 2A and 2B). Because of the patient's age, location of lesion, its clinical characteristics (pigmented expansive mass) and location (upper maxillary middle line), the first clinical diagnosis option for surgery was MNTI. However, within differential diagnoses, the radiologists considered the possibility of an odontogenic or developmental cyst due to the defined and expansive radiolucent image observed in the anterior area of the maxilla.

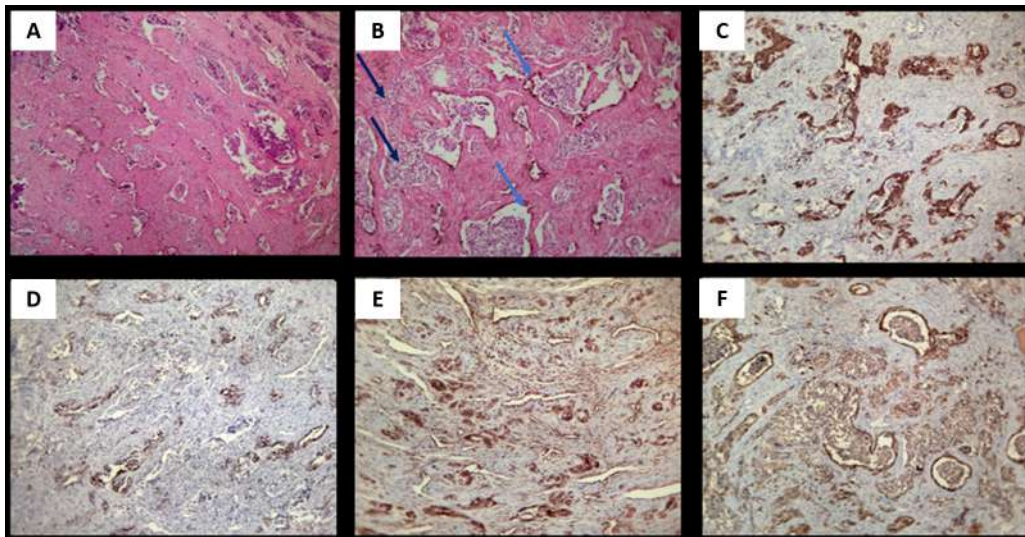


Figure 2. Histology and immunohistochemistry of the Melanotic Neuroectodermal Tumor of Infancy. A). Panoramic view: fibrous stroma, tumor cells are grouped into alveoli and nests. (H&E coloration, X40 magnification). B). Zoom showing that the alveoli are peripherally coated with pigment-laden melanocytes (light blue arrows point to melanocytes), small, round cells with hyperchromatic nucleus can be seen inside; these are neuroblastic, grouped in nests and also in the stroma. (Dark blue arrows point to neuroblast nests) (H&E coloration, X40 magnification). C). Positive marker for HMB45 immunohistochemistry. Melanocytic marker. Cytoplasmic marker (Magnification X40). D). Positive marker for immunohistochemistry protein S100, melanocytic marker. Cytoplasmic marker (Magnification X40). E). Positive marker for immunohistochemistry CD99, neuroectodermal marker. Membrane marker. (Magnification X40). F). Positive marker for immunohistochemistry NSE (enolase), neuroectodermal marker. Cytoplasmic marker (Magnification X40) (HOMI Case)

Source: by the authors

The immunohistochemistry markers with positive results were: HMB45, cytoplasmic marker, marking melanocytes (Figure 2C), protein S100, cytoplasmic marker, melanocytic (Figure 2D), CD99 membrane marker, marking neuroblastic cells (Figure 2E) and enolase (NSE), cytoplasmic marker, neuroectodermal (Figure 2F), which were monitored. This set of microscopic (morphology) and immunohistochemical characteristics determined the final diagnosis of Melanotic Neuroectodermal Tumor of Infancy (MNTI).

The patient was initially given weekly postoperative clinical and imaging checks during the first month, followed by monthly follow-ups, and annual orthopedic management-supported checks are currently carried out for further reconstruction by the Oral and Maxillofacial Surgery Service.

DISCUSSION

Melanotic Neuroectodermal Tumor of Infancy (MNTI), first described in 1918 by Krompecher, reporting 215 cases since 1992, is a rare, pigmented, benign, locally aggressive, recurrent, and possibly malignant neoplasm with metastatic capacity. Histologically, it has a three-phase pattern of fibrous stroma, cell population grouped in alveoli and solid nests, which belongs to the group of small round blue cell tumors of neuroectodermal nature.^{2,7,8} In the pediatric population, these include small, round cell tumors, Ewing's sarcoma/PNET, embryonic rhabdomyosarcoma, lymphoblastic lymphoma,^{8,11} small cell desmoplastic tumor, mesenchymal chondrosarcoma, Neuroblastoma (Table 1), small cell osteosarcoma, and Wilms tumor.¹⁰

MNTI has been associated with a mutation of the BRAF V600E gene.¹² The Raf-MEK-ERK mitogen activates the protein kinase pathway, which is triggered by growth factors, hormones and cytokines that regulate the proliferation, differentiation, survival, senescence, and migration of tumor cells. Mutations of gene BRAF V600E have been identified in cells derived from the neural crest and large cells containing melanic pigment, which is based on the finding that the oncogenic mutation of BRAF V600E is a fundamental event in the melanotic neoplasia group, often defining diploid tumors and other aneuploids.¹²

Different theories have been described for its etiology: congenital melanocarcinoma derived from impacted epithelial remains, odontogenic epithelium and a phylogenetic origin.^{10,13} However, one consensus states that it originates from the neural crest. In 1969, Borello and Gorlin demonstrated the neuroectodermal origin of this tumor by histopathological analysis, as the cells resemble neuroblasts. Electron microscopy studies showed neurosecretory granules and detected high urinary levels of vanillylmandelic acid (VMA).^{10,12-14}

It occurs most often in men (58%) than women (38.7%). The average age is before the end of the first year of life^{4,5,15} and the preferred anatomical sites are the cranio-maxillo-facial skeleton: midline maxillary bone (68%-80%), skull (10.8%), mandible (5.4%) as the case described in the present clinical case, in which the premaxilla and left maxillary portion were affected, extending to the floor of the nostrils. It may also occur in other sites, including brain, epididymis, mediastinum, ovary, uterus and the appendicular skeleton in femur.^{1,7, 8,16-18}

Clinically, it appears as a sessile-based, asymptomatic, unique, non-ulcerated, firm lesion, with increased lobular volume and pigmentation (blue, black or brown) that may or may not be seen in the soft tissue covering it.^{2,10} It shows an expansive, rapid growth, producing destruction of underlying bone, and possibly associated with displacement and alteration in dental development,^{7,11,15,16} invading neighboring anatomical structures such as the nasal cavity, orbit and base of the skull, as found in the patient of this case, with the mentioned tumor characteristics and extension to nostrils, and the need to remove dental germs.

Radiographically in CT, MNTI shows as a defined isodense lesion, causing the expansion and destruction of cortical bone, simulating "floating" teeth (when presented in the maxillaries), sometimes associated with a sunburst spiculated periosteal reaction. The soft tissue component appears slightly hyperdense, which is attributed to melanin.² In magnetic resonance, this tumor appears isointense or hypointense in the T1 and T2-enhanced sequences, showing improvement in contrast after gadolinium injection; the large amount of melanin pigment explains a T1-enhanced hyperintense sequence. The tumor may also contain areas of T1 and T2-enhanced hypointense sequences, corresponding to hyperostosis and calcifications.^{2,7,10}

Macroscopically, the tumor appears as a multilobed soft mass that varies in color from grayish to dark blue depending on the amount of melanin pigment.¹⁸ Histopathologically, it shows a three-phase pattern consisting of fibrous-bottomed stroma and cells that architecturally are grouped in alveolar pattern and nests. The alveoli are marginally coated by melanocytes that are large cuboidal cells loaded with

melanin pigment; light retains groups of small, round cells of neuroblastic nature that are similarly grouped into solid nests in the stroma and can show cell crushing, or Azzopardi phenomenon, which is caused by the fall of DNA from the nucleus,^{6,8} as shown in the histological images.

Electron microscopy has shown the presence of desmosomes, melanosomes and neurosecretory granules that is correlated with the expression of markers of epithelial, melanocytic and neuroectodermal in immunohistochemistry: CKAE1/AE3, Melan A, HMB45, protein PS100, SOX10, CD99, CD57 (LEU-7), NSE: (enolase) and synaptophysin.^{10,18-19}

Diagnosis should be established comprehensively considering clinical, imaging, pathological, ultrastructure, immunohistochemical, and molecular characteristics. The morphological interpretation and immunophenotypic expression in the present case guided the diagnosis with positivity for HMB45 and PS100 given the melanocytic differentiation, as well as positivity for CD99 and NSE (enolase) in small neuroblast-type cells.

Usually, the tumor has a benign, locally aggressive behavior, with recurrence of 10% to 15%, being eventually malignant in 6.97%, and acquiring metastatic capacity due to the proliferation of neuroblastic cells, with metastasis described in regional lymph nodes, liver, pleura, bone marrow, and pelvis.^{7,8,11,14-17,20}

The perpetuation or involution of MNTI can be explained by the relationship of the stroma and its inflammatory infiltrate composed mainly of T lymphocytes, CD4 and CD8 regulators, dendritic cells presenting antigens and macrophages. At the onset of the tumor process, the inflammatory infiltrate is rich in

M1 macrophages with a TH1 response; such response activates CD4 and CD8 T cells, producing tumor cell apoptosis, indicating that the TH1 or M1 response is antitumor or protective in nature. However, the tumor growth process and the production of IL-10 exceeds the tumor protection capacity deranging the TH1 response into TH2 or with M2 macrophages, providing the lesions with recurrence and progression characteristics. This mechanism is possibly related to the action of IL-10 on neuroblastic cells, increasing the expression of CD138 and leading to the activation of FGF2, which causes neoplastic proliferation and adhesion of malignant cells to the extracellular matrix, prevents mobility, and allows for increased cell invasion and metastasis. Removing much of the tumor allows a greater infiltration of TH1; for this reason, in many cases the lesion involves without the need for complete resection.²¹

There is no real consensus regarding the management of MNTI. However, the treatment of choice is surgical resection with adequate safety margins^{3,22,23} as done in the present case. In cases in which the tumor affects the head and/or neck, or the jaws, proper margin resection is an important issue due to potential damage to neurovascular anatomical structures; when full resection cannot be achieved, chemotherapy with cyclophosphamide, doxorubicin, vincristine, etoposide, or carboplatin has been reported as an adjuvant treatment option to reduce recurrence rate,^{3,22-23} considering that chemotherapy is not a common treatment procedure, except in patients with confirmed metastasis and previously assessed by oncology.¹⁰

Small-molecule drugs targeting BRAF or MEK kinases have been approved for the treatment of BRAF mutation in melanoma,

including the immune checkpoint inhibitor Ipilimumab, selective type 1 BRAF: Vemurafenib and Dabrafenib and the MEK inhibitor Trametinib. Treatment with these drugs has shown to be effective in decreasing tumor size, but the resistance is a problem in the management of melanoma. This drug resistance can be triggered by the genomic instability that leads to tumor heterogeneity, involved in cancer progression. Since MNTI is a benign tumor, the use of BRAF targets treatments with a greater chance of success represent a potential alternative in treatments for aggressive tumors with BRAF mutations.¹²

This finding is important in understanding the biology of MNTI; however, caution should be exercised because there are very few reports of pediatric patients with BRAFV600E mutant tumors successfully treated with Vemurafenib, which has shown to be safe in clinical trials of melanoma, but there are significant side effects with its use, ranging from rash, arthralgia, nausea, squamous cell carcinoma and liver damage.¹²

CONCLUSION

This case illustrates the benefit of multidisciplinary integration, as it shows the importance of taking into account variables of the clinical, imaging, pathological, and immunohistochemical expressions that help establish a correct diagnosis and ensure adequate therapeutic management, in addition to a continued presentation of new cases of this rare pathology.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

CORRESPONDING AUTHOR

Claudia Patricia Peña Vega
Universidad Nacional de Colombia

cppenav@unal.edu.co
Carrera 51 # 104-B38 Apartamento 402
(+57) 3014553002
Bogotá, Colombia

REFERENCES

1. El-Naggar AK, Chan JKC, Grandis JR, Takashi T, Slootweg PJ. WHO classification of head and neck tumours. 4th ed. 2017. Lyon: International Agency for Research on Cancer, 2017.
2. Moreau A, Galmiche L, Minard Colin V, Rachwalski M, Belhous K, Orbach D et al. Melanotic neuroectodermal tumor of infancy (MNTI) of the head and neck: a French multicenter study. *J Craniomaxillofac Surg*. 2018; 46(2): 201–6. DOI: <https://doi.org/10.1016/j.jcms.2017.12.001>
3. Pinheiro T, Carneiro J, Alves S, Pinheiro J, Tuji F. Melanotic neuroectodermal tumor of infancy in an African-indigenous patient from the Amazon: a case report. *Head Face Med*. 2013; 9-35. DOI: <https://dx.doi.org/10.1186%2F1746-160X-9-35>
4. Ubale P, Baldwa N, Gujjar P. Anaesthetic management of a neuroectodermal tumor of infancy: A rare case report. *Anesth essays Res*. 2017; 11(1):251–53. DOI: <https://dx.doi.org/10.4103%2F0259-1162.186863>
5. Gupta R, Gupta R, Kumar S, Saxena S. Melanotic neuroectodermal tumor of infancy: review of literature, report of a case and follow up at 7 years. *J Plastic Reconstr Aesthet Surg*. 2015; 68(3): e53-4. DOI: <https://doi.org/10.1016/j.bjps.2014.12.014>
6. Mendis B, Lombardi T, Tilakaratne W. Melanotic neuroectodermal tumor of infancy: a histopathological and immunohistochemical study. *J Investig Clin Dent*. 2012; 3(1): 68–71.
7. Yildirim G, Çalişkan , Akça C, Dolanmaz D, Toy H. Melanotic neuroectodermal tumor of infancy in the maxilla: a case report. *Int J Pediatr Otorhinolaryngol Extra*. 2011; 6(4): 351–4.
8. Kruse-L sler B, Gaertner C, B rger H, Seper L, Joos U, Kleinheinz J. Melanotic neuroectodermal tumor of infancy: systematic review of the literature and presentation of a case. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2006; 102(2): 204–16. DOI: <https://doi.org/10.1016/j.tripleo.2005.08.010>
9. Andrade N, Mathai P, Sahu V, Aggarwal N, Andrade T. Melanotic neuroectodermal tumour of infancy: a rare entity. *J oral Biol Craniofacial Res*. 2016; 6(3): 237–40. DOI: <https://dx.doi.org/10.1016%2Fj.jobcr.2016.06.005>
10. Unsal H, Yalcin M. Melanotic neuroectodermal tumor of infancy in the maxilla. *J Craniofac Surg*. 2018; 29(1): e28–30. DOI: <https://doi.org/10.1097/SCS.0000000000003993>
11. Tam J, Cheung W, Senger C, Reichman M, Campbell JM. Melanotic neuroectodermal tumour of infancy in the maxilla: a case report. *Can Dent Assoc*. 2015; 7(81).
12. Gomes C, Diniz M, de Menezes G, Castro W, Gomez R. BRAFV600E mutation in melanotic neuroectodermal tumor of infancy: toward personalized medicine? *Pediatrics*. 2015; 136(1): e267-9. DOI: <https://doi.org/10.1542/peds.2014-3331>
13. Ju rez L, Cruz A, Medina C. Tumor neuroectod rmico melanoc tico de la infancia: presentaci n de un caso. 2013; 12(3): 201–4.
14. De Souza P, Merly F, Maia D, Castro W, Gomez R. Cell cycle-associated proteins in melanotic neuroectodermal tumor of infancy. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 1999; 88(4): 466–8. DOI: [https://doi.org/10.1016/s1079-2104\(99\)70063-6](https://doi.org/10.1016/s1079-2104(99)70063-6)

15. Bangi B, Tejasvi M. Melanotic neuroectodermal tumor of infancy: a rare case report with differential diagnosis and review of the literature. *Contemp Clin Dent*. 2012 ; 3(1): 108–12. DOI: <https://dx.doi.org/10.4103%2F0976-237X.94559>
16. Fakuade B, Adeoye J. Melanotic neuroectodermal tumor of infancy: a rare presentation of an extremely rare neoplasm and diagnostic implications in Gombe, Nigeria. *Pan Afr Med J*. 2017; 28: 5. DOI: <https://dx.doi.org/10.11604%2Fpamj.2017.28.5.9394>
17. Goldblum J, Folpe A. *Enzinger and Weiss's: soft tissue tumors*. Philadelphia: EL Servier, Saunders; 2014.
18. Barrett AW, Morgan M, Ramsay AD, Farthing PM, Newman L, Speight P. A clinicopathologic and immunohistochemical analysis of melanotic neuroectodermal tumor of infancy. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2002; 93(6): 688–98. DOI: <https://doi.org/10.1067/moe.2002.124000>
19. Borello E, Gorlin R. Melanotic neuroectodermal tumor of infancy—a neoplasm of neural crest origin. Report of a case associated with high urinary excretion of vanilmandelic acid. *Cancer*. 1966; 19(2): 196–206. DOI: [https://doi.org/10.1002/1097-0142\(196602\)19:2%3C196::aid-cnrcr2820190210%3E3.0.co;2-6](https://doi.org/10.1002/1097-0142(196602)19:2%3C196::aid-cnrcr2820190210%3E3.0.co;2-6)
20. De Souza PE, Merly F, Mai DM, Castro WH, Gomez RS. Cell cycle-associated proteins in melanotic neuroectodermal tumor of infancy. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 1999; 88(4): 466–8. DOI: [https://doi.org/10.1016/s1079-2104\(99\)70063-6](https://doi.org/10.1016/s1079-2104(99)70063-6)
21. Stieder L, Carlos R, Le n JE, Ribeiro A, Costa V, Kaminagakura E. Protumorigenic M2-like phenotype cell infiltration in the melanotic neuroectodermal tumor of infancy. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2016; 121 (2): 173-9. DOI: <https://doi.org/10.1016/j.oooo.2015.09.015>
22. Maroun C, Khalifeh I, Alam E, Akl P, Saab R, Moukarbel RV. Mandibular melanotic neuroectodermal tumor of infancy: a role for neoadjuvant chemotherapy. *Eur Arch Otorhinolaryngol*. 2016; 273(12) :4629–35. DOI: <https://doi.org/10.1007/s00405-016-4066-6>
23. Murphy C, Pears J, Kearns G. Melanotic neuroectodermal tumour of infancy: surgical and chemotherapeutic management. *Ir J Med Sci*. 2016; 185(3): 753–6. DOI: <https://doi.org/10.1007/s11845-015-1323-4>
24. Wu X, Shankar S, Munday WR, Malhotra A. Melanotic neuroectodermal tumor of infancy. *J Clin Neurosci*. 2016; 31: 205-207. DOI: <https://doi.org/10.1016/j.jocn.2016.02.023>