Melanotic Neuroectodermal Tumour of Infancy (MNTI) is a rare neoplasm typically reported in infancy, involving the head and neck regions. Although described as a benign tumour, the growth is rapid and has a high local recurrence rate. Due to the rapid and locally destructive growth, it can easily be misdiagnosed as a malignant tumour, leading to unwarranted and potentially harmful interventions. Therefore, histopathological assessment is pertinent in confirming the diagnosis. Early surgical resection is critical to limiting cosmetic disfigurement but is challenging as it requires prompt and careful planning to ensure optimal clearance. Therefore, it is crucial to approach anterior maxillary swellings in an infant with an index of suspicion and to consider MNTI as a rare but important differential diagnosis to ensure a timely diagnosis and plan for appropriate early intervention. We report a case of an infant presenting with a rapidly growing and locally destructive intra-oral swelling who underwent tumour excision and was later confirmed to be MNTI. We discuss the clinical, radiological, and histological features and the challenges in diagnosing and managing this rare childhood tumour.

Abstract
Melanotic Neuroectodermal Tumour of Infancy (MNTI) is a rare neoplasm typically reported in infancy, involving the head and neck regions. Although described as a benign tumour, the growth is rapid and has a high local recurrence rate. Due to the rapid and locally destructive growth, it can easily be misdiagnosed as a malignant tumour, leading to unwarranted and potentially harmful interventions. Therefore, histopathological assessment is pertinent in confirming the diagnosis. Early surgical resection is critical to limiting cosmetic disfigurement but is challenging as it requires prompt and careful planning to ensure optimal clearance. Therefore, it is crucial to approach anterior maxillary swellings in an infant with an index of suspicion and to consider MNTI as a rare but important differential diagnosis to ensure a timely diagnosis and plan for appropriate early intervention. We report a case of an infant presenting with a rapidly growing and locally destructive intra-oral swelling who underwent tumour excision and was later confirmed to be MNTI. We discuss the clinical, radiological, and histological features and the challenges in diagnosing and managing this rare childhood tumour.

Introduction
Melanotic Neuroectodermal Tumour of Infancy (MNTI) is a rare, benign neoplasm usually described in early infancy. Since its first description in 1918 by Krompecher, this neoplasm has been given numerous terminologies: retinal anlage tumour, congenital melanocarcinoma, melanotic progonoma and pigmented congenital epulis [1]. The variability in nomenclature was due to the uncertainty of the tumour’s origin until later proposed by Borello and Gorlin in 1966 to have originated from the neural crest cells [2]. This was supported by the detection of vanillylmandelic acid (VMA) in some patients with this tumour, consistent with those neoplasms of neuroectodermal origin, such as pheochromocytoma and neuroblastoma [3].

Though recognized as a benign tumour, its rapid expansile growth and potential to cause local destruction and tissue cell invasion into the bone render it more threatening than perceived. Furthermore, some literatures have cited a 10-60% recurrence rate after surgical resection [4]. Due to mimicking features of malignant neoplasms and the lack of awareness of this rare tumour, MNTI can be challenging to diagnose clinically, leading to treatment delay, which can complicate surgical decisions.

We present a case of an infant with a rapidly growing maxillary MNTI associated with local bony invasion and nasal passage occlusion, which was successfully excised and with good post-operative recovery on follow-up.

Case Presentation
An eight-month-old girl was referred to our centre for an enlarging left maxillary swelling. She was born term to non-consanguineous parents. She is the only child with no family history of malignancy.
or heritable genetic disorders.

At five months old, a peanut-sized swelling was initially noticed at the upper left alveolar ridge. She was brought to a primary healthcare clinic, was reassured to be ‘normal,’ and would gradually self-resolve. However, three months later, the lesion grew rapidly for a week, causing left facial swelling. There were no obstructive airway symptoms, and her oral feeding was unaffected.

She was promptly referred to the oral and maxillofacial surgeon. On examination, she was well-thrived with no dysmorphic features. A well-circumscribed, non-tender, firm, greyish mass of approximately 3cm x 3cm in size was seen extending from the left alveolar ridge to the midline of the hard palate, resulting in a left maxillary swelling. The surrounding mucosa was pink, with no ulceration, bleeding, or discharge.

Other systemic examinations and baseline blood investigations were unremarkable.

An urgent magnetic resonance imaging (MRI) of the head showed a lobulated, soft tissue mass measuring 2.5cm x 1.5cm x 4.3cm, which demonstrated an isointense signal on T1-weighted (TW1) sequence and hyperintensity on T2-weighted (TW2) and Short Tau Inversion Recovery (STIR) sequences relative to the adjacent muscles. It extends superiorly into the left nasal cavity, obliterating the inferior nasal meatus and abuts the inferior turbinate. The adjacent hard palate was thinned out. Inferiorly, the mass bulged into the oral cavity and indented onto the left hemitongue. Anteriorly, the mass extended between the unerupted teeth, displacing them, and causing an anterior bulging of the left upper lip [Figure 1(A-D)].

Figure 1 (A-D). (A) Axial TW1 scan shows an isointense signal (yellow arrow), while on (B) TW2 scan, a hyperintense (red arrow) lobulated soft tissue mass can be seen occupying the left anterior half of the hard palate, extending into the midline. The lesion also displaces the unerupted deciduous teeth on the left jaw. (C) The coronal TW1 scan shows an isointense signal lesion (yellow arrow) and (D) hyperintense on STIR coronal image (red arrow). The mass extends superiorly into the left nasal cavity, obliterating the inferior nasal meatus and abuts the left inferior turbinate.
She underwent an excision of the tumour two days later. A circumferential mucosal incision was made along the tumour margin to expose the palatal bone, maxillary alveolus, and buccal side of the inferior maxilla, followed by osteotomy of these sites. Tooth follicles 61 to 65 confined within the alveolus were removed along with the tumour. The margins of the tumour were sampled to assess for tumour cells. She made an uneventful recovery in the ward and could feed orally on day three postsurgery. A year on, during her latest review, her wound had healed well with no evidence of tumour recurrence [Figure 2(A-D)]. The mastication, deglutition and speech functions are uninterrupted despite the surgical defect, with just mild cosmetic defect [Figure 3(A-B)].

Figure 2(A-D). (A) Pre-operative lesion, a greyish, smooth, non-ulcerated lesion extending into the soft palate and superiorly into the left maxilla. (B) The intra-operative picture showed the osteotomised palatal bone and maxillary alveolus with the tumour excised with the tooth follicle. (C) The oral mucosa and palate were well healed at three months post-operation. (D) On review at one-year post-operation, the surgical site was well healed but showed missing dentition over the upper left quadrant.
Figure 3(A-B). (A) Pre-operative picture shows left facial swelling with loss of the nasolabial fold and bulging of the left upper lip. (B) Three months post-operative picture shows left upper lip collapse and contraction with mild facial deformity.

The excised tumour tissue grossly measured 36mm x 25mm x 20mm with a central brownish nodule [Figure 4(A)]. Microscopic examination showed an infiltrative tumour arranged in tubules and clusters surrounded by fibrocollagenous stroma [Figure 4(B)]. The tumour showed two populations of neoplastic cells; the smaller cells exhibited small round nuclei with scanty cytoplasm, whereas the larger cells displayed enlarged nuclei with the presence of melanin pigments and located mainly at the periphery of the tumour nests [Figure 4(C)]. The neoplastic cells were seen infiltrating the adjacent bony tissue and into the inter-trabecular spaces. All the excisional margins were clear of tumour cells.

Immunohistochemical stains revealed that the large epithelioid cells were positive for AE1/AE3 and HMB45 [Figures 4(D) and (E)]. The small neuroblast-like cells, on the other hand, stained positive for CD56 and synaptophysin [Figure 4(F) and (G)]. Immunopositivity with neuron specific enolase (NSE) were seen in both population of cells [Figure 4(H)]. The biphasic neoplastic cells on microscopic assessment, along with the immunohistochemistry findings, confirm the diagnosis of MNTI.
Figure 4(A-H). (A) Gross appearance of the excised tumour showing areas of dark pigmentation. (B) Tumour cells are arranged in clusters within the fibrocollagenous stroma [H&E, 2x]. (C) The small neuroblast-like cells with hyperchromatic nuclei in the centre (orange arrow) are surrounded by larger, melanin-producing cells at the periphery (red arrow) [H&E, 20x]. Immunohistochemistry: (D) AE1/AE3 and (E) HMB45 immunopositivity are seen in the larger cells at the periphery of the tumour nests [5x]. The small cells are positive for (F) CD 56 [5x] and (G) synaptophysin [10x]. (H) Neuron specific enolase positivity is evident in both the large and small cells [10x].
Discussion

MNTI is typically seen in infants less than six months of age, commonly involving the craniofacial regions and with a majority affecting the maxilla [5]. Mandibular, cranial, cerebral and genitalia involvement are less commonly reported [4, 5]. These tumours usually present with a unilateral, painless, non-ulcerated mass that may be seen from birth and is mostly associated with a recent rapid lesion expansion. They are well-circumscribed and bluish-grey due to the melanin pigment, but this may not always be clinically evident [6]. Though benign, these lesions can grow rapidly, causing significant local destruction; hence, any delay in treatment may result in more challenging surgical resection and disfigurement.

The tumour in this patient presented as a fast-growing lesion with local mass effect, suspicious of a malignant neoplasm, although she was clinically well with no constitutional symptoms. A broad clinical differential diagnosis for a rapidly growing anterior maxillary swelling needs to be considered [Table 1]. Most odontogenic lesions are benign and more commonly seen in adults than children. Anterior maxillary swelling seen in young children is often more likely to be aggressive than benign; hence warrants a more thorough assessment and consideration for an earlier referral [7]. Unfortunately, diagnosing the lesion based on appearance alone is clinically challenging. However, features such as onset from infancy, painless, non-ulcerated and bluish-grey pigmentation should trigger the suspicion of MNTI and narrow the list.

Imaging is essential to determine the extent of the tumour growth and skeletal involvement, thus providing a sound basis for surgical planning [10]. On MRI, the findings should follow the paramagnetic effects of melanin. However, as described by Haque et al. in their cohort, the lesions are predominantly iso- or hypointense on TW1 and TW2 scans, contrary to the expected findings [11]. In our case, the tumour showed isointensity on TW1 and hyperintensity on TW2 imaging. This altered paramagnetic effect could probably be explained by the variable amount of the connective tissue stroma, uneven melanin deposition or the maturity of the melanosomes present [11, 12]. Computed tomography (CT) can delineate the bony involvement more accurately than MRI, but the radiation risk should be weighed against how significantly this will aid the management.

Nonetheless, there is a limitation in these imaging modalities to help differentiate MNTI from other anterior maxillary swellings confidently. Some authors have recommended testing for urinary catecholamines and VMA, which is raised in 10-15% of cases, given its neuroectodermal origin [13]. However, due to the low yield, the test provides little value in diagnosing MNTI.

Biopsy is the gold standard for diagnosis. Microscopically, MNTI consists of biphasic cell clusters which are pretty distinctive and unique, separating it from other malignant small round blue cell neoplasms such as lymphoma, primitive neuroectodermal tumour (PNET)/Ewing sarcoma, melanoma and rhabdomyosarcoma. The dual cell population consists of larger epithelioid cells at the periphery with melanin and smaller neuroblast-like cells at the centre. The larger cells are immunoreactive for cytokeratin, HMB45, epithelial membrane antigen (EMA), vimentin, NSE, synaptophysin and Leu7, whereas the neuroblast-like cells show positivity for synaptophysin, CD56, glial fibrillary acidic protein (GFAP) and NSE [4, 7, 14, 15]. Furthermore, the biphasic morphology and negative immunoreactivity towards S-100, leukocyte common antigen (LCA) and muscle markers such as desmin and myogenin will rule out other similar tumours from the differential diagnoses [4, 12]. In our case, the immunohistochemistry findings are consistent with the other published reports and confirm the diagnosis.

Surgical excision is the recommended treatment for MNTI, but the amount of margin clearance has been debated between different authors. Though benign, MNTI has a relatively high risk of recurrence, which may result from incomplete tumour excision, multifocal lesions or seeding during the surgery [12, 16]. While a complete resection seems to confer the most reliable cure, it is associated with more cosmetic disfigurement and damage to functionally relevant structures [16, 17]. However, a French multicenter study showed that the recurrence rate did not correlate with the resection status [18], and a successful outcome can also be achieved with a more conservative approach and microscopically incomplete resection [16, 17]. Nevertheless, this difficult decision should always be balanced between the risk of incomplete clearance versus compromising the aesthetic and
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<th>Lesions/Tumours</th>
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| Eruption cyst [8]                             | • Soft tissue counterpart of dentigerous cyst  
• Common in newborns and associated with the eruption of natal teeth.  
• Appears soft, translucent and blue to purple-brown swelling of the gingiva. |
• Present at birth and may grow rapidly.  
• Usually pedunculated mass.  
• Size may be large to cause feeding or breathing difficulty in young infants. |
| Infantile fibrosarcoma [7]                    | • Malignant neoplasm affecting infants and children less than two years.  
• Rapidly growing soft tissue mass.  
• May ulcerate and associated with tooth displacement/bone invasion.  
• Affects the head and neck region in 10% of cases. |
| Rhabdomyosarcoma                              | • Rapidly growing, malignant neoplasm of the skeletal muscles.  
• Primarily seen in children <5 years of age, with a predilection for the head and neck regions, and rarely intra-oraly.  
• May initially be painless and cause tooth mobility as the lesion expands. |
| Burkitt’s lymphoma                            | • May present with gingival swelling or rapidly growing tumour mass.  
• Non-specific clinical presentation (prolonged fever, cervical lymphadenopathy, facial swelling and pain) may be mistaken for odontogenic infections.  
• Tooth displacement and ulceration may occur. |
| Fibrous epulis / pyogenic granuloma [7, 9]     | • Benign, reactive lesion.  
• Pink, non-inflamed and firm mass. Pyogenic granuloma may appear reddish/bluish with ulcer.  
• Most often painless and grows from the gingival free margins.  
• More commonly seen in adults and older children. |
| Ameloblastic fibroma [8]                      | • Common in the first two decades of life.  
• Large tumours are expansile lesions, while smaller ones appear asymptomatic.  
• Tends to affect the posterior mandible more commonly.  
• Appears as a unilocular or multilocular radiolucency which is often associated with an unerupted tooth. |
| Dentigerous cyst [8]                          | • Intrabony cyst originates from the dental follicle of an unerupted tooth.  
• Common in 2nd-3rd decades of life.  
• Asymptomatic or can cause painless expansion of the jaws.  
• Radiographically, the cyst appears as a unilocular radiolucency encircling an impacted tooth. |
| Peripheral giant cell granuloma               | • Benign, soft tissue purplish-red nodule.  
• Occurs due to trauma or local irritation.  
• More commonly seen in older adults.  
• Bony erosion may be seen in some cases. |
| Adenomatoid odontogenic tumour                | • Anterior maxillary swelling associated with unerupted or impacted tooth, especially the canine.  
• Peripheral variant is rare and mainly on the anterior maxillary gingiva.  
• Benign, painless, non-invasive and slow growing, but may displace... |
function, especially in anatomically sensitive sites where future reconstruction may be problematic.

Given the tumour’s rarity, the optimal management for inoperable, relapsing or disseminated disease is less established. The malignant potential of the tumour is attributed to the neuroblastic-like component and hence may be regarded as a mimic of neuroblastoma. Chemotherapy employed in the treatment of neuroblastoma has been utilised in the treatment of more aggressive MNTI [4]. Neoadjuvant chemotherapy has been used in primarily inoperable tumours by shrinking the lesion to allow better surgical access, thus reducing the risk of mutilating surgeries [4, 16]. Metastatic disease is reported in up to 2% of cases and can spread widely, resulting in death [16]. Unfortunately, the response to chemotherapy in this group is poor, and the outcome is often unfavourable. Nonetheless, the exact role of chemotherapy in the treatment of MNTI still needs further evaluation.

Clinical follow-up after treatment, whether surgical intervention alone or combined with chemotherapy, is paramount. Children diagnosed with MNTI before two months of age are at higher risk of recurrence and thus will require much closer surveillance than those diagnosed after 4.5 months [5]. Similarly, those with incomplete margin clearance and conservatively managed will require frequent clinical review and surveillance imaging, especially in the initial six months when most recurrences occur [16-18]. Although the risk of recurrence is low with clear surgical margins seen in our patient, regular reviews by the multidisciplinary teams are still necessary, especially by the dental team, to ensure good oral function, such as chewing and swallowing, before a more definitive reconstruction of the maxillary alveolus and missing dentition can be offered later.

In conclusion, pigmented anterior maxillary swelling in infants should be regarded cautiously and referred appropriately if in doubt. MNTI is a rare but important differential diagnosis in a rapidly growing maxillary tumour seen in infancy, mainly if it is painless, non-ulcerated and with bluish-grey pigmentation. Early diagnosis and intervention are crucial in MNTI to limit the extent of surgery and disfigurement. Finally, close clinical follow-up and multidisciplinary management should be emphasized, especially in the first-year post-intervention, due to its relatively high recurrence rate and malignant potential.

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