Clinics in Diagnostic Imaging (90)

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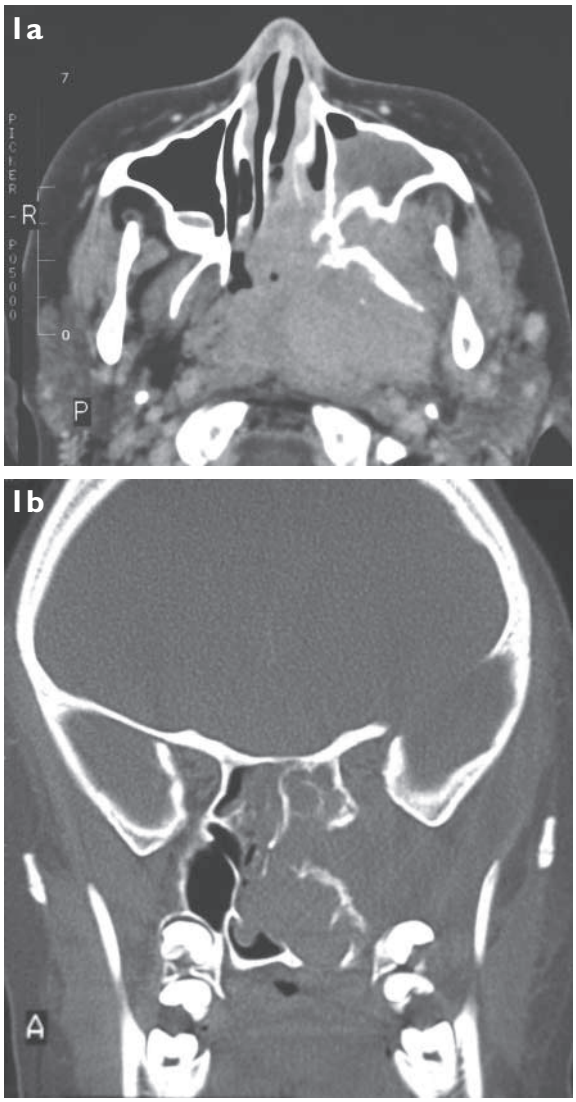

Fig. 1a Enhanced axial (soft tissue window) and (b) coronal (bone window) CT scans of the nasopharynx.

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CASE PRESENTATION

An 11-year-old Malay boy presented with intermittent epistaxis from his left nostril as well as left facial numbness for four months. He had been diagnosed to have tonsillitis and left otitis media four months earlier, for which left myringotomy and tonsillectomy were performed. A left nasal polyp was then noted intra-operatively. There was otherwise no recent injury or other medical history of note. On examination, a bleeding soft tissue mass was seen in the left nasal cavity. He was haemodynamically stable although he had a low haemoglobin level of 9.5 g/dl on admission. No cervical lymphadenopathy was palpable. Radiographs were not performed. Computed tomography (CT) was performed (Figs. 1a and 1b). What do these show? What is the diagnosis?

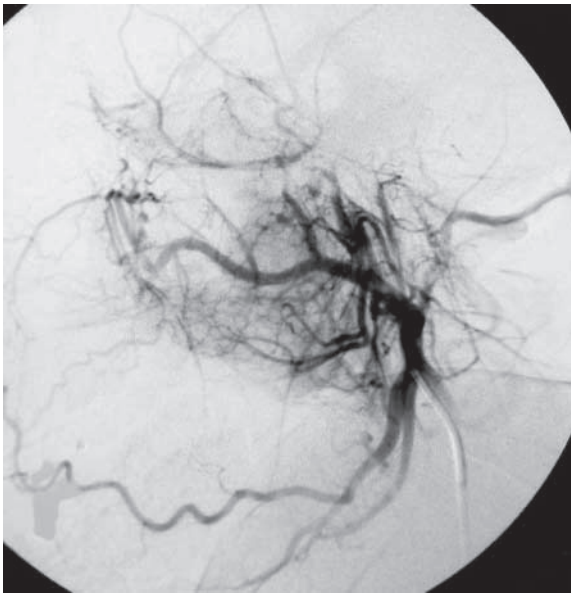

Fig. 2 Left external carotid angiogram (lateral view) shows a vascular mass with mild tumour staining in the nasopharyngeal region. The blood supply is mainly from branches of left internal maxillary and ascending pharyngeal arteries. Preoperative embolisation using polyvinyl alcohol particles was subsequently performed.

IMAGE INTERPRETATION

Enhanced axial and coronal CT scans show a large tumour in the left side of the nasopharynx. The tumour has moderately intense and homogeneous enhancement. Extension into the left parapharyngeal and masticator spaces is present. The tumour extends anteriorly into posterior part of left nasal cavity with displacement of the nasal septum. There is anterior bowing of the posterior wall of left maxillary sinus consistent with the bone remodelling effect due to a slow-growing tumour (Fig. 1a). Gross expansion of the left pterygopalatine fossa and destruction of the left pterygoid bone are also noted. The left inferior orbital fissure is widened. There is also invasion into the sphenoid sinuses (Fig. 1b).

Based on the clinical features and CT scan findings, the tumour was initially thought to represent a juvenile nasopharyngeal angiofibroma. Tumour embolisation was performed (Fig. 2) followed by surgical resection. A dumbbell shaped tumour was noted intra-operatively. The anterior part of the tumour mass was successfully removed but the posterior part of the tumour mass was found to be adhered to the surrounding tissue and was therefore not completely resectable. Histopathological examination revealed an undifferentiated nasopharyngeal carcinoma. Immunohistochemistry and in-situ hybridisation were strongly positive for Ebstein-Barr virus (Figs. 3a-c).

DIAGNOSIS

Childhood nasopharyngeal carcinoma.

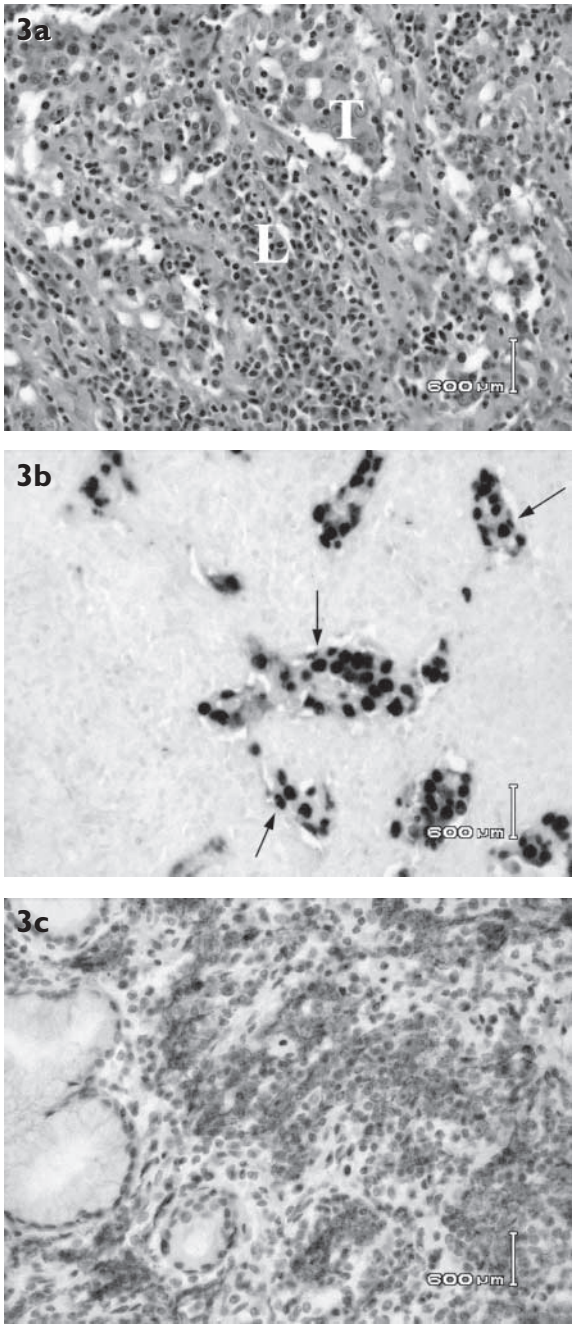

Fig. 3 Histopathological study of the nasopharyngeal mass. (a) Photomicrograph shows proliferation of cuboidal or polygonal shaped tumour cells (T) against a background of lymphoid infiltration (L). There is absence of keratinisation. (Haematoxylin and eosin stain) (b) In-situ hybridisation to detect EBV-encoded nuclear RNAs was positive (arrows). (c) Immunohistochemistry was positive for latent membrane protein-1, an EBV-transforming protein, expressed in almost two thirds of EBV-positive NPC.

CLINICAL COURSE

Magnetic resonance (MR) imaging performed post-operatively showed residual tumour in the nasopharynx, sphenoid sinuses, left parapharyngeal space and left masticator space. There was intracranial extension but no intralesional flow void was detected (Figs. 4a-c).

Further tumour work-up, which included radioisotope bone scan and CT of the thorax and

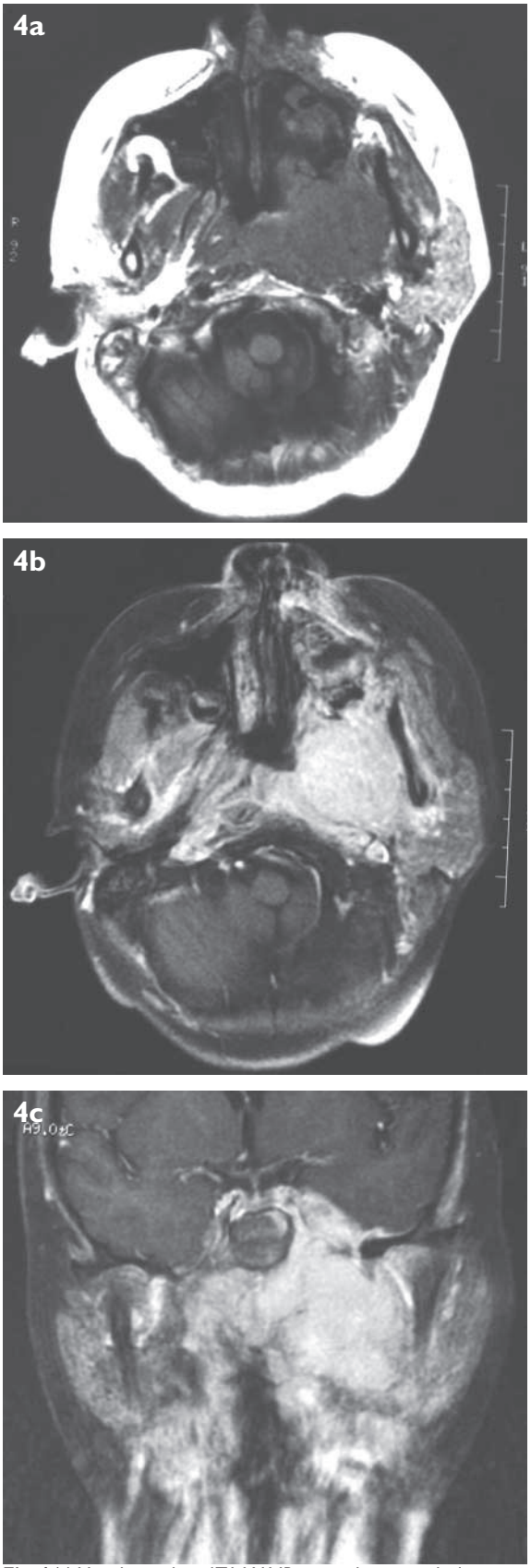

Fig. 4 (a) Unenhanced axial T1-W MR image shows residual tumour in the left pterygopharyngeal and parapharyngeal regions. The lesion is isointense to muscle, but hypointense to cerebellar grey matter. (b) Enhanced fat-suppressed axial T1-W MR image shows homogeneous enhancement of the tumour. (c) Enhanced fat-suppressed coronal T1-W MR image shows residual tumour in the left pterygopharyngeal region with left cavernous sinus and intracranial extensions.

Table 1. World Health Organisation (WHO) histological classification of NPC.

Type	Histology
I	keratinising squamous cell carcinoma
II	non-keratinising carcinoma
III	undifferentiated carcinoma

abdomen, did not reveal any evidence of distant metastasis. The patient is currently undergoing radiotherapy and chemotherapy.

DISCUSSION

Malignant tumours of the nasopharynx are rare and account for 1-3% of all paediatric malignancies[1]. In children, nasopharyngeal carcinoma (NPC) accounts for only 20-50% of nasopharyngeal malignancies[2,3]. This contrasts with adults whereby almost all nasopharyngeal malignancies are carcinoma. In children, the majority of nasopharyngeal malignancies are parameningeal rhabdomyosarcoma (RMS) or lymphoma, usually the non-Hodgkin type. NPC has a bimodal age distribution. It is most common in those aged 60-80 years. About 5% to 12% of NPC occur below 30 years of age[4,5]. It affects male children twice as often as females. It is more common in Southeast Asian and black American children. In Southeast Asia, Malay children are the second most commonly affected, after Chinese children[6]. Genetic and environmental factors predispose these children to increased risk of NPC, namely deletions of chromosomes, mutations and specific HLA types[2] and infection with EBV.

Childhood NPC is different from adult type as the former is more frequently associated with Ebstein-Barr virus infection[2]. The childhood NPC variant is almost always undifferentiated carcinoma (WHO type 3) (Table I) in contrast to the squamous cell carcinoma (WHO type 1) in the elderly[2,4,7]. The childhood variant is also highly responsive to chemo- and radiotherapy, but has a higher rate of locoregional and distant metastases[1,3,8].

The most common presenting symptom of childhood NPC is a painless cervical mass (70-90%), which is bilateral in 50% of cases[7,9]. Clinical and radiological evidence of nasopharyngeal disease may therefore be absent[2]. The other signs and symptoms of childhood NPC are non-specific, ranging from serous otitis media, rhinorrhoea, otalgia to trismus. These symptoms are common in children and are usually associated with benign conditions. The duration of symptoms can last up to two years, and a long duration is usually associated with advanced disease[2]. In disseminated advanced NPC, paraneoplastic conditions such as hypertrophic osteoarthropathy,

Table II. Differential diagnoses of childhood nasopharyngeal masses.

	Childhood NPC	Angiofibroma	Rhabdomyosarcoma	Lymphoma
Age (in years)	10 to 30	5 to 25	<12 (peak 2-5)	2 to 20
Male:female ratio	2 to 1	almost exclusively in males	1 to 1	
CT Enhancement				
- intensity	moderate	very intense	moderate	moderate
- pattern	homogeneous	homogeneous	heterogeneous	homogeneous
- skull base invasion	92%	20-36%	18%	common
MR imaging				
- T1 signal intensity (compared to muscle)	slightly high	iso	iso	iso
- T2 signal intensity (compared to muscle)	slightly high	high	high	high
- Enhancement	moderate homogeneous	very intense homogeneous flow voids +	moderate heterogeneous	moderate homogeneous
Lymphadenopathy	80-90%	nil	12-50%	50-98%

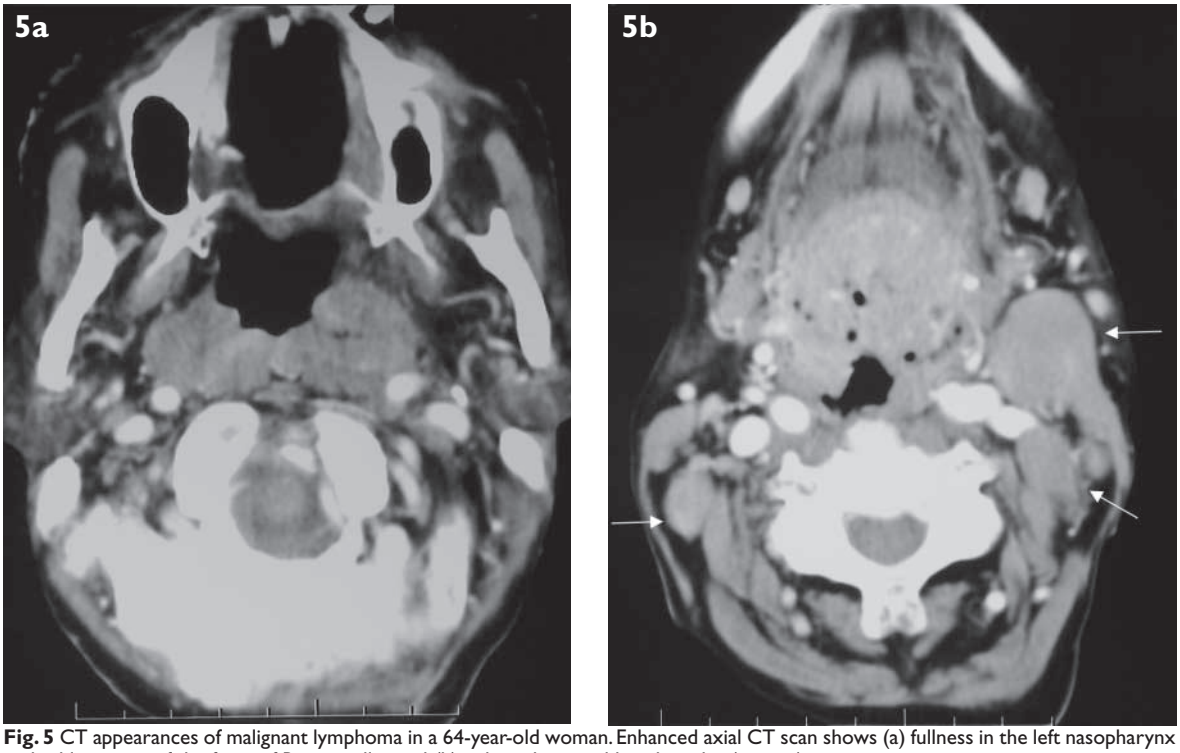

Fig. 5 CT appearances of malignant lymphoma in a 64-year-old woman. Enhanced axial CT scan shows (a) fullness in the left nasopharynx with obliteration of the fossa of Rosenmuller and (b) enlarged cervical lymph nodes (arrows).

pyrexia of unknown origin and syndrome of inappropriate secretion of antidiuretic hormone have been described[2]. A possibility of nasopharyngeal malignancy should be raised in any child with rapidly increasing nasal obstruction, when signs and symptoms persist more than three weeks despite treatment and when unilateral otitis media occurs with cervical lymphadenopathy[5,10]. Other symptoms such as headache and cranial nerve palsies (usually involving the trigeminal and abducens nerves) may indicate skull base invasion.

Both CT and MR imaging are used for preoperative assessment of NPC, especially because deep extension is not easily seen clinically. Six percent of NPC is undetected at endoscopy[11]. Endoscopic examination of the nasopharynx is also difficult in children because of their small size and uncooperative nature. CT is able to demonstrate the extent of bony destruction while MR imaging has the advantage of multiplanar capability and excellent soft tissue contrast. MR imaging also obviates irradiation of young children and is superior to CT in post-operative surveillance.

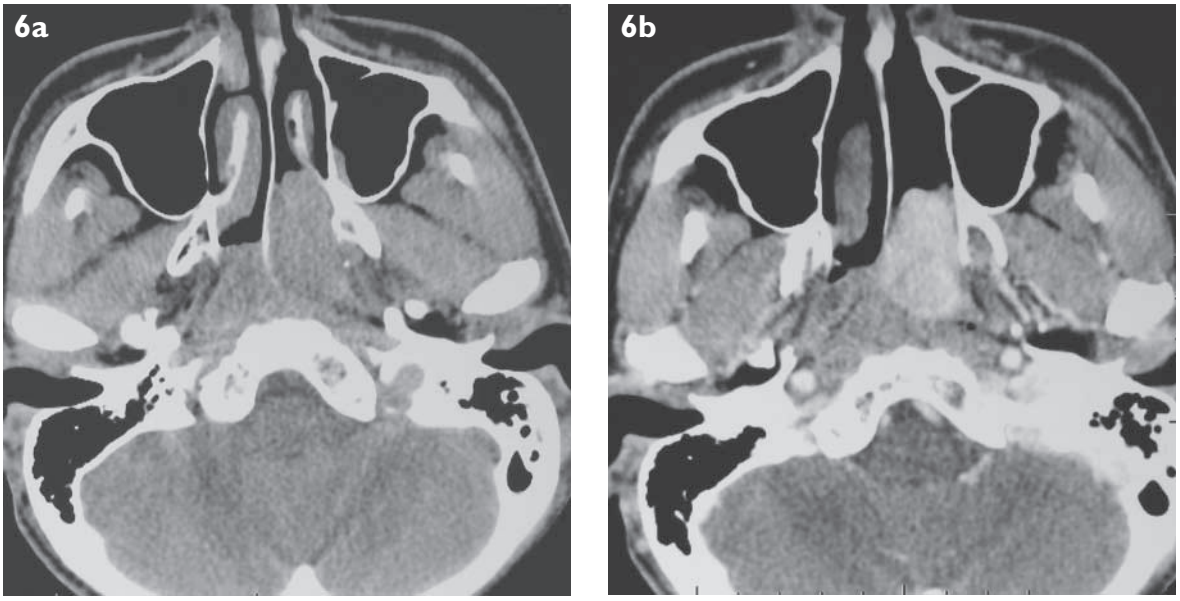

Fig. 6 CT appearances of juvenile nasopharyngeal angiofibroma. (a) Unenhanced and (b) enhanced axial scans show a mass in the left nasopharynx, which extends into the nasal cavity, and demonstrates intense homogeneous enhancement.

On CT, 82% of NPC arise in the posterolateral recess of the pharyngeal wall (usually the fossa of Rosenmuller) and 12% arise in the midline[12]. The latter may be confused with a benign retention cyst or Thornwaldt cyst[13]. On CT and MR imaging, childhood NPC typically shows homogeneous, moderately intense enhancement of the primary tumour and metastatic lymph nodes.

On T1-weighted MR images, childhood NPC shows signal intensity equal to or higher than muscle in 75%; and is higher in signal intensity than muscle but lower than cerebellar grey matter on T2-weighted images[14]. Because of its aggressive nature, NPC can even extend to the brain stem, which worsens the prognosis. Unusual sites of involvement such as calvaria, dura, suprasellar region and brain stem can be seen at the initial presentation or in cases that have been previously irradiated[13]. One of the most severe complications of NPC is invasion of the carotid sheath with pseudoaneurysm formation, which is more common after radiotherapy. At presentation, 5-11% of cases have distant metastases. The distant metastases include the bone (67%), lungs (20%), liver (30%), bone marrow (23%) and mediastinum[2]. The most common lymph nodes involved are the jugulodigastric, upper and middle jugular in the anterior cervical chain.

Childhood NPC can be differentiated from NPC in the elderly. In the latter presentation of NPC, the primary tumour and metastatic lymph nodes appear heterogeneous with greater tendency to necrosis on CT and MR imaging[15]. This phenomenon is probably related to different histological types. Childhood NPC may also be differentiated from the other more common nasopharyngeal malignancies, namely, parameningeal RMS and malignant lymphoma (Figs. 5a-b). In malignant lymphoma, there is usually homogeneous moderate enhancement on CT, similar to NPC[15-17]. However on MR imaging, the signal intensity is low to intermediate on T1-weighted images and moderately high on T2-weighted images[9]. The skull base involvement in lymphoma tends to be more permeative compared to the outright destruction seen in NPC[16,17]. There is also usually concomitant lymphadenopathy beyond the region of the head and neck in lymphoma.

Heterogeneous enhancement or signal intensity on CT or MR imaging is more suggestive of RMS than childhood NPC[15-17]. Intratumoral haemorrhage is reported to be atypical of RMS although histopathologically, they are also reported to bleed. Lymphadenopathy is also less common in RMS as compared to childhood NPC, occurring in 12-50%[16,17]. Bone erosion occurs less frequently in RMS. In RMS and non-Hodgkin lymphoma, metastases to the marrow are frequent. The parameningeal site of RMS increases the likelihood of meningeal involvement. The important clinical and imaging differences among the various childhood nasopharyngeal masses are listed in Table II.

Besides malignancy, the differential diagnoses of nasopharyngeal masses in children also include benign lesions and inflammatory conditions. Adenoiditis is common in children and may spread to the retropharyngeal nodes resulting in suppurative lymphadenitis and abscess formation. Inflammation of the nasopharynx may also occur secondary to malignant otitis externa, retropharyngeal and submandibular abscess[18]. Of the benign tumours, juvenile nasopharyngeal angiofibroma (JNA) is the most significant lesion that needs to be differentiated

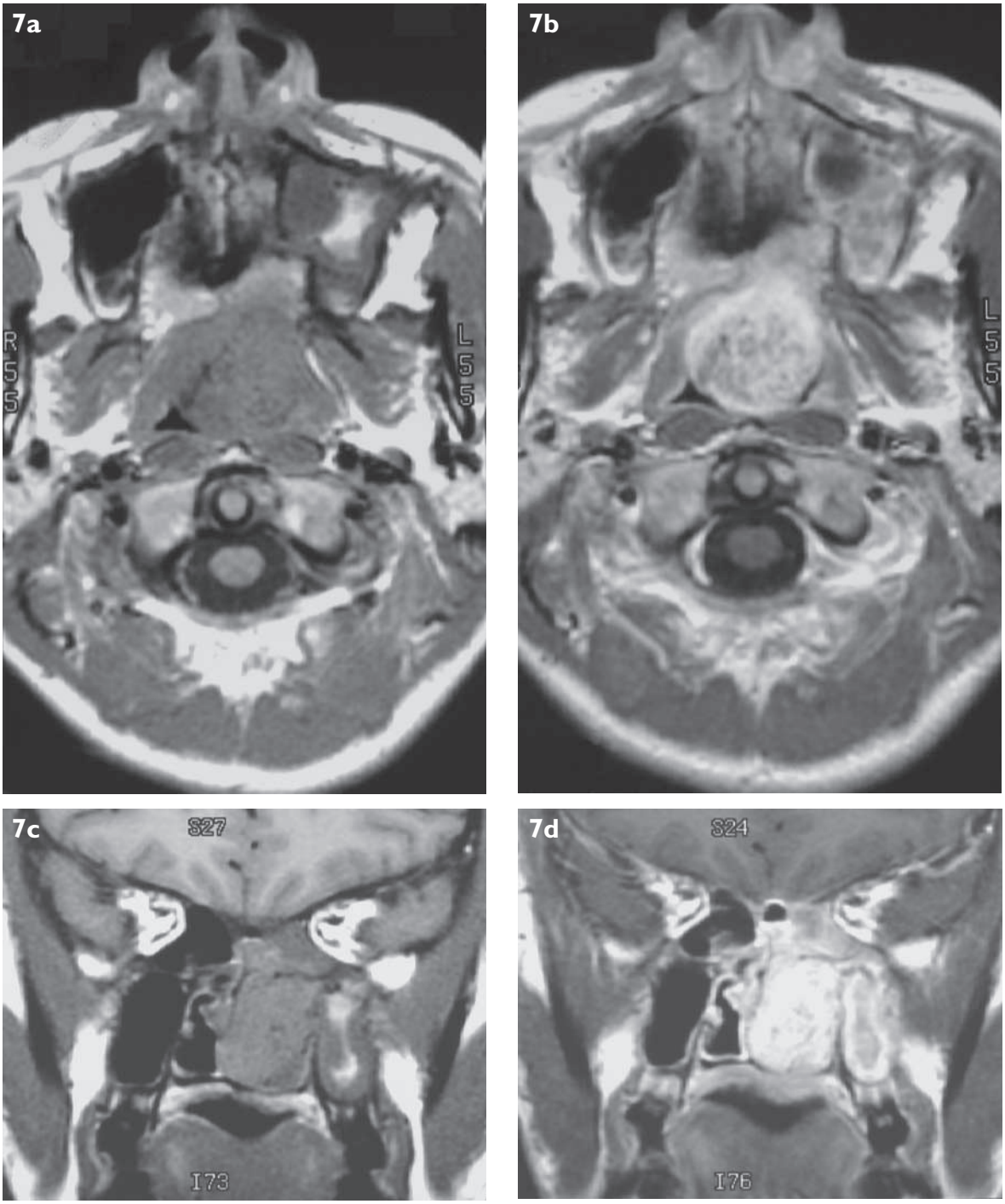

Fig. 7 MR imaging appearances of juvenile nasopharyngeal angiofibroma. (a) Axial T1-W MR image shows a mass in the nasopharynx that is isointense to muscle. (b) Enhanced axial T1-W MR image shows intense enhancement of the mass with intra-lesional flow voids. (c) Coronal T1-W MR image shows an isointense (to muscle) mass that extends into left sphenoidal sinus. (d) Enhanced coronal T1-W MR image shows intense enhancement of the mass with intra-lesional flow voids.

from nasopharyngeal malignancies. Other benign lesions include haemangioma, schwannoma, neurofibroma, germ cell tumour, rhabdomyoma, antrochoanal polyp, encephalocoele, inverting papilloma and branchial cyst.

JNA, a rare benign tumour, presents similarly to childhood NPC. It originates in the superior margin of the sphenopalatine foramen. Enlargement of the sphenopalatine foramen is pathognomonic of JNA[19]. On coronal CT, the two diagnostic features of JNA are a mass in the pterygoplatine fossa and erosion of the root of the medial pterygoid plate[20]. Involvement of the pterygopalatine fossa occurs in 90% of cases[18]. As it is a locally-aggressive tumour, it shares features with nasopharyngeal malignancies such as extension into the nasal cavity, and spread via fissures and foramina into the infratemporal fossa, orbital apex, middle cranial fossa and cavernous sinus. Like the malignant tumours, it also shows bony changes, of

which there are two types. One is a simple pressure erosion of the pterygoid base (40%) and the other involves invasion and expansion of the pterygoid base and greater wing of sphenoid bone (60%)[19]. Intracranial extension occurs in 10-20% of all JNA[21]. Anterior bowing of the posterior wall of the maxillary antrum, the "antral sign", seen in about 50% of JNA, is however, not unique to JNA, occurring in other slow growing neoplasms such as schwannoma.

JNA can be differentiated from nasopharyngeal malignancies as it typically shows very intense and homogeneous enhancement on both CT (Figs. 6a-b) and MR imaging (Figs. 7a-d). Intralesional signal flow voids due to its highly vascular stroma are seen on MR imaging[22]. In JNA, angiography is performed when preoperative embolisation is indicated. On carotid angiography, JNA typically shows intense vascular staining with accumulation of contrast persisting into the capillary phase without early draining veins. Extracranial JNA derives its blood supply mainly from the internal maxillary and ascending pharyngeal arteries. In intracranial lesions, it may derive supply from the internal carotid artery.

There are two main systems for staging of NPC, namely the American Joint Committee for Cancer staging system/TNM system (1997)[7] and the Ho classification, which also describes the location of clinically involved cervical lymph nodes[23]. Childhood NPC is believed to have a better prognosis compared to the elderly type[14]. Conventional treatment with high dose radiotherapy has shown a cure rate of only 30-60% due to systemic disease and late side effects of radiation[2,7,24]. Of radiological importance, the late side-effects in survivors include impaired growth, chronic sinusitis, otitis media, pneumonia, hypoplasia of facial bones, osteoradionecrosis of mandible and encephalopathy. Second malignancies have been reported to occur in 6-8%, such as salivary mucoepidermoid carcinoma of the base of tongue and parotid gland, osteosarcoma and chondrosarcomas[2,24]. Chemotherapy is essential for treatment of non-apparent micrometastases[1]. A long-term survival rate of 50-70% has been reported in combined therapy[8]. Intensity modulated radiotherapy (IMRT) is expected to improve local tumour control and decrease long-term side effects.

At the present time, no pediatric malignancies are routinely imaged with (18) F-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET) for diagnosis, staging or follow-up after therapy. The usefulness of PET in children is assumed to be similar to adults. In normal children, there is prominent FDG activity seen in the thymus and neck[25]. In adults, the main advantages of FDG-PET in NPC would be in the assessment of lymph node and distant body metastases; and for the early detection of recurrent tumour. PET is reported to be more accurate than MR imaging for the detection of residual or recurrent tumour with a negative predictive value of 100% compared with 70% for MR imaging[26]. The recommended optimum time for performing PET after radiotherapy is six months or later[27]. Image fusion of PET with CT (or PET/CT) has been shown to be useful to discriminate between pathological and physiological lesions as well as for pre-biopsy localisation.

ABSTRACT

An 11-year-old boy presented with a nasopharyngeal mass that was thought to represent a juvenile angiofibroma based on the initial clinical and radiological evaluation. Partial tumour resection was performed. Resected specimen revealed histological diagnosis of undifferentiated carcinoma. Further evaluation of the tumour including MR imaging, radioisotope bone scan, CT thorax and abdomen were performed. Differential diagnoses of childhood nasopharyngeal masses were discussed. The differences between childhood NPC and adult NPC, rhabdomyosarcoma, malignant lymphoma and juvenile nasopharyngeal angiofibroma were also discussed.

Keywords: childhood nasopharyngeal carcinoma (NPC), computed tomography (CT), magnetic resonance (MR) imaging, angiography

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