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Case Report

Advanced stage nasopharyngeal carcinoma in children

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ABSTRACT

Nasopharyngeal carcinoma (NPC) is common in adult and elderly population, however, the incidence among children is still very low worldwide. Due to its rarity and non-specific clinical presentation, the diagnosis in children is often delayed and misinterpreted. The difficulty in reaching the final diagnosis was related to its hidden anatomical location, raising challenges in performing endoscopy and biopsy in children to obtain the precise histopathologic feature. We reported two cases on nasopharyngeal carcinoma in children with two different peculiar complaints. The first patient was 12 years old boy who complained of multiple recurrent unilateral masses on the left neck and history of nosebleeds with an unknown history of the previous histopathology features of the neck masses obtained by complete surgical neck mass removal beforehand. The second patient was 15 years old boy with main complaint of chronic headache, accompanied by doubled vision with apparent family history of malignancy, particularly nasopharyngeal carcinoma. Based on the history of illness, physical examination, imaging, and histopathology, we concluded that both patients were diagnosed with advanced stage nasopharyngeal carcinoma with different types of histopathologic feature.

Keywords: Nasopharyngeal carcinoma, Malignancy, Children, Pediatric

INTRODUCTION

NPC is an extremely rare malignancy among pediatric age group. This rarity makes the diagnosis quite difficult and often associated with delayed diagnosis which may lead to advanced loco-regional disease. The annual incidence of NPC in pediatric age group is around 0.5 per million children ranging between the age of 10-14 years old.[1] This incidence is less than 1% of all pediatric malignant lesions. NPC is extremely rare among children regardless of the different regions in the world, also NPC represents 2% of the head and neck malignant neoplasm in pediatric age group. As it is rare in the pediatric group and its non-specific clinical presentation that caused delayed diagnosis on the basis of the initial thinking of benign etiologies or other common inflammatory disease.[1]

CASE REPORT

This was a case report of two unusual cases of pediatric nasopharyngeal carcinoma that presented to the outpatient clinic with advanced stage and non-specific clinical presentations. The complexity of the medical and family history and clinical symptoms makes the diagnosis difficult, associating with delayed diagnosis and treatment. Here we studied the clinical presentations, risk factor and the diagnostic challenges in the management of pediatric nasopharyngeal cancer.

Case 1

A 12 years old boy was referred to the ENT outpatient clinic Dr. Sardjito Hospital from pediatric outpatient

clinic with a main complaint of multiple unilateral neck masses in 3 months duration, progressively increasing in size. He also had history of recurrent nosebleed from both nostrils. There was no history of chronic cough, fever or other constitutional symptoms. The parents declared that there was a history of similar main complaint about 3 years ago with no improvement after 14 days of antibiotic and steroid therapy, therefore complete surgical removal of the neck mass was done but the result of the acquired specimen of the neck mass was unknown. There was no family history of malignancy. The patient had a habit of consuming salted fish and preservative food since toddler.

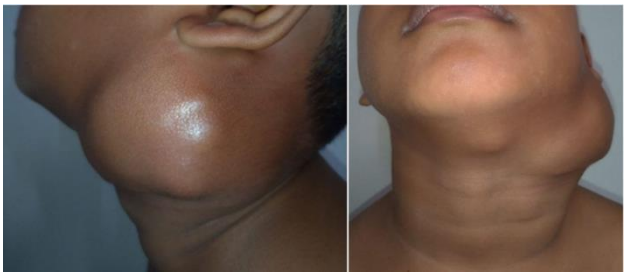

Figure 1: Left unilateral multiple level II-III neck masses.

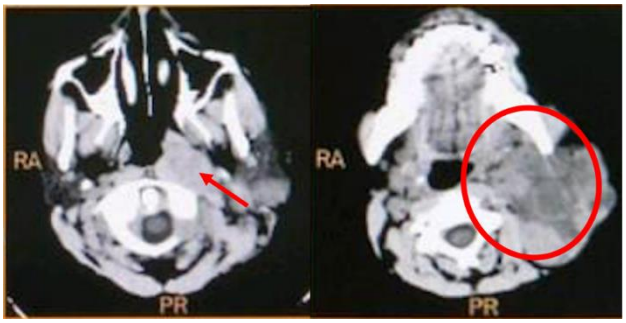

Figure 2: CT scan of the nasopharynx using contrast showed left unilateral lobulated neck masses (circle) and soft tissue mass at the left nasopharynx (arrow).

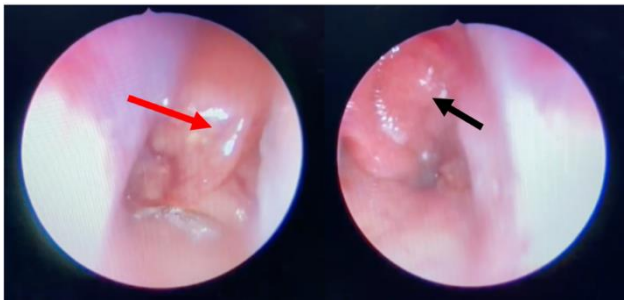

Figure 3: Nasopharyngeal endoscopy showed mass filled left nasopharyngeal region (black arrow) and thickening of right nasopharyngeal region (red arrow).

The patient was initially referred from pediatric outpatient clinic with differential diagnosis of tuberculous lymphadenitis, lymphoma and metastatic carcinoma. Complete blood examination showed no abnormality, Mantoux test was negative, and the fine needle aspiration biopsy (FNAB) of the neck masses showed feature of metastatic undifferentiated carcinoma. He then was referred to our clinic for further investigation of the primary tumor.

Physical examination revealed multiple unilateral neck masses located at the level II and III on the left side. It measured 7×4×2 cm and 3×2×1 cm on the left level II, 4×3×2 cm on the level III. Nasopharyngeal endoscopy showed a glimpsed of mass filled left nasopharyngeal region, the examination could not obtain clear appearance of the mass because the patient was not so cooperative. Therefore, we planned the patient for nasopharyngeal endoscopy under general anesthesia followed by biopsy.

Contrast MSCT of the neck mass showed an aggressive appearance of soft tissue mass in the nasopharynx with infiltration of the left para pharyngeal space and into the left carotid space. There were multiple lobulated enlarged lymph nodes on the left sides of the upper neck. Chest radiograph was normal and abdominal ultrasound yielded normal result.

Examination of rigid nasopharyngeal endoscopy under general anesthesia was done and the findings revealed fragile, rough-surfaced, non-vascular mass occupying about 90% of the left nasopharyngeal region. Biopsy of the nasopharyngeal mass was taken and sent for histopathological examination, which confirmed the feature of undifferentiated carcinoma. The patient then diagnosed with undifferentiated nasopharyngeal carcinoma with the staging of T2N3M0 stage IVA according to American Joint Committee of Cancer Guideline 8th edition. He was then referred to the oncology and radiotherapy department for further neoadjuvant chemotherapy followed by concomitant chemoradiotherapy.

Case 2

A 15 years old boy was admitted to ENT outpatient clinic Dr. Sardjito Hospital from district hospital due to 3 months of chronic headache and doubled vision. The patient had no history nosebleed, ear symptoms, or visible neck mass. He had already received pain medication for his chronic headache for the last 3 weeks from the district hospital but no significant improvement, then referred to the ENT clinic for evaluation of possible ENT infection or abnormality in anatomical structure. Further investigation revealed that the patient had significant family history of malignancy. Two of his uncles from his mother side suffered from nasopharyngeal carcinoma at young age and died soon after the diagnosis was determined, and another uncle suffered from colorectal cancer, also from his mother side. From his father side, one aunt died from vertebral malignancy. His grandfather also died from malignant

disease but the parent couldn't recall specifically what the malignancy was.

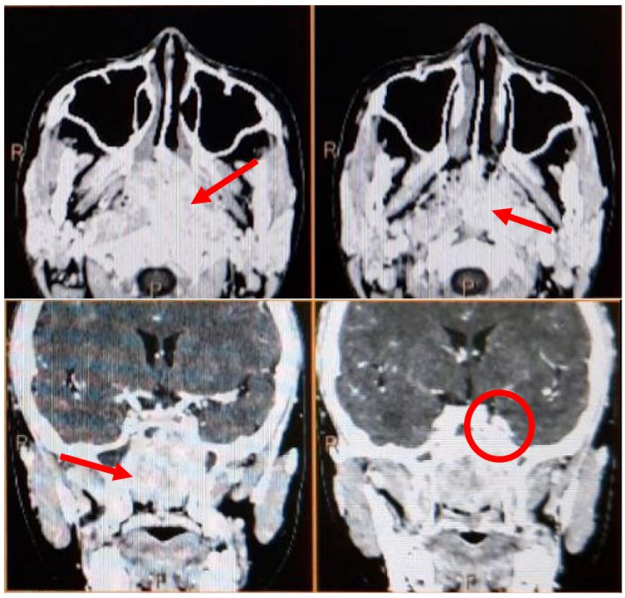

Figure 4: CT scan of the nasopharyngeal using contrast showed infiltrating soft tissue mass (red arrow), and intracranial extension (red circle).

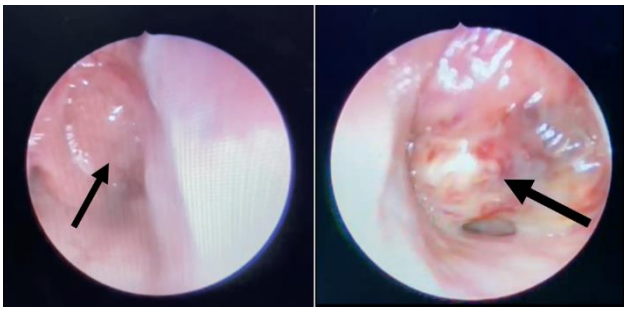

Figure 5: Nasopharyngeal endoscopy showed bilateral nasopharyngeal mass (arrow).

Physical examination of the anterior rhinoscopy, otoscopy, and oropharynx showed no abnormality, however, palpation of the neck discovered multiple bilateral neck masses at the level II and III. The mass was measured 2×1 cm and 2×2 cm on the right side, and 3 small masses on the left side with each dimension of 2×1 cm. The neck masses were quite deep, therefore cannot be detected through inspection alone. This neck mass finding led us to suspect if there's a possibility of nasopharyngeal carcinoma or lymphoma in this patient. We could suspect the possibility of tuberculous lymphadenitis but there was no history of fever, cough, or any other breathing disorder.

Head and neck MSCT with contrast was done and showed an infiltrative contrast-enhanced soft tissue mass of the left and right nasopharyngeal regions with extension to the intracranial, also into para pharyngeal space and pterygopalatine fossa, which could explain the chronic headache and the doubled-vision. The MSCT also confirmed the multiple bilateral neck masses from the physical examination.

Unlike the first patient, this patient was quite cooperative for rigid nasopharyngeal endoscopy and biopsy in the outpatient setting. We found rough-surfaced, non-vascular mass filling the left nasopharyngeal region with minimal bleeding. Biopsy of the nasopharyngeal mass was taken and sent for histopathological examination, which confirmed the feature of non-keratinizing squamous cell carcinoma, undifferentiated subtype. After the biopsy procedure, the patient experienced a minor complication in the form of nosebleed from the left nostril, so we inserted anterior nasal gauge with antibiotic ointment to control the bleeding, the gauge was removed 24 hours later. We also sent the patient to do ultrasound guided fine needle aspiration biopsy at the neck mass and found feature of metastatic non-keratinizing squamous cell carcinoma. The patient then diagnosed with non-keratinizing nasopharyngeal squamous cell carcinoma, undifferentiated subtype with the staging of T4N3M0 stage IVA. He was also referred to the oncology and radiotherapy department for further neoadjuvant chemotherapy followed by concomitant chemoradiotherapy.

DISCUSSION

NPC is a very rare pediatric malignancy contributing for less than 1 % of all pediatric neoplasms.[1] NPC arises from the epithelial cells of the nasopharyngeal wall.[1] The first peak of incidence is 10-20 years old with median age of 13 years old at diagnosis. Age distribution was different in each area. The high-risk region for nasopharyngeal carcinoma was Southern China, Taiwan, and Hongkong.[1,2] NPC represents around 2% of the head and neck area and makes up 1-5% of all pediatric cancer and 20-50% of all primary malignant nasopharyngeal tumor in children.[2,3] Generally, in Indonesia, it is very rare to find early stage of NPC. The youngest patient found was 13 years old and the oldest was 79 years old, according to the study in Abidin, General Hospital Banda Aceh in the late 2019.[4]

NPC is pathologically classified into three categories according to WHO classification: keratinizing squamous cell carcinoma (type I), non-keratinizing squamous cell carcinoma (type II), and undifferentiated carcinoma (type III). Majority of the case are undifferentiated carcinoma at the advanced stage. NPC is usually caused by genetic susceptibility, environmental factors like exposure to chemical, carcinogen, or infection.[5] Like any other form of malignancy, it is believed to have multifactorial etiology comprises of genetic predisposition, epigenetic alteration related to Epstein Bars virus (EBV) combined with exposure to environmental factors.[5,6] Compared to adults, pediatric NPC is biologically more aggressive and generally diagnosed in advanced stage. In low incidence area, younger case of NPC tends to be familial cases,

undifferentiated type suggesting that NPC may develop through exposure to environmental factors such as EBV infection in early life in genetically susceptible individual.[5,6]

In both our cases, this multifactorial theory might be justified. Even though the environmental factor was not quite clear, we can assume that the first patient may develop risk of NPC from his dietary habit in consuming salted and preserved food since he was toddler on the daily basis. Previous study had mentioned the role of various salted and preserved foods could also had been associated with NPC in regions of Asia and Africa country.[7,8]

Our second case showed possibility of genetic predisposition in the form of epigenetic alteration related to EBV. Studies have shown the role of EBV infection in the occurrence of nasopharyngeal malignant lesion. This EBV could be transferred through familial DNA.[8] Family history had shown multiple history of NPC and other cancer that might be caused by EBV risk factor.

NPC commonly occurs in adolescent male children. The most common presentation of NPC in children is unilateral or bilateral bulky cervical lymphadenopathy, although nosebleed, nasal congestion, and obstruction may be the earliest manifestation of NPC which often remain unrecognized. NPC presents locoregional advanced disease, larger primaries, and higher nodal stage in children compared to adults. When the disease invades the base of the skull it may lead to headache, cranial nerve palsy, and raised intracranial pressure which is rarely described in pediatric case.[8,9] Because NPC arises in deep region of the nasopharynx, it remains asymptomatic for a long time and the diagnosis is often made at an advanced local stage.[9,10]

Nasal endoscopy and biopsy of the mass or the cervical lymph node helps in confirming the diagnosis. Histopathology examination is mandatory for the diagnosis of NPC.[9,10] An asymptomatic lesion that appears to be an enlarged lymph node creates a difficult dilemma for the primary care physician. Usually, the parents are anxious for a diagnosis and an intervention. Most cases of lymphadenopathy are self-limited and require only observation and patience. Enlarged lymph nodes that are rubbery, firm, immobile, or that persist for longer than six weeks or enlarge during a course of antibiotics should be evaluated by a head and neck surgeon, and a biopsy is recommended.[9,10,11]

Our first case had proved that performing an endoscopy in children with suspected intranasal pathology imposed more challenges. Making the child to stay still for the endoscopic procedure to be performed inflicts its own difficulty, therefore, for our first patient, we must plan endoscopic evaluation and biopsy under general anesthesia in the operating room. This procedure might cause more risk of side effect from the anesthetic procedure. In order to obtain the precise tissue with positive result of malignancy, we requested an accompaniment from the pathologic anatomy department to observe the specimen right away. As mentioned before, the risk of bleeding from the biopsy was higher in children than in adults because of the smaller size of the nasal cavity that give rise to more risk of trauma from the maneuver. This happened to our second patient right after the biopsy and we had to insert nasal gauge for 24 hours to control the bleeding.

Investigations and imaging studies are performed in order to assess the disease stage, the extend of the primary tumor and locoregional spread, and possible skull base, major cervical vessels, and nerve involvement. Clinical locoregional evaluation should include full clinical examination including cervical supraclavicular lymph nodes and neurological evaluation. Computerized tomography (CT) of the head and neck may help delineating skull base erosion by the disease.[10,11] Staging of NPC is based on the American Joint Committee on Cancer (AJCC) 8th edition system.[11] Both our case showed advanced stage of NPC, CT evaluation of the nasopharyngeal area had helped to explain the cause of the main symptom especially for our second patient where we found out that there's an intracranial and retroorbital extension that could explain the chronic headache and doubled-vision.

On the other hand, the first patient might show up with pretty common feature NPC which is a multiple unilateral bulky neck mass. But the recurrent history of the neck masses could mislead the initial suspected diagnosis, moreover, the histopathology feature of the previous neck masses was unknown. It was a possibility that the previous neck masses that happened 3 years ago had already been a sign of early NPC, but because of the lack of education, awareness, and knowledge the diagnosis could not be determined beforehand. If malignancy was suspected in a neck mass case with hard, firm or rubbery consistency, fixed supraclavicular mass, lymph node larger than 2 cm in diameter, persistent enlargement for more than two weeks, no decrease in size after four to six weeks, absence of inflammation, present of ulceration, failure to respond to antibiotic therapy, or accompanied by a thyroid mass, the patient should be referred to a head and neck surgeon for urgent evaluation and possible biopsy.[11,12]

The treatment of pediatric NPC had undergone several changes in the last few decades. Until the early 1990's, patients were mostly treated by irradiation, but then chemotherapy was introduced.[12] Besides the stage of the disease at the commencement of the therapy, the survival rates for young patients are generally better than in adults. The histological Type III which are more common in children possess a higher degree of radio sensitivity and local radio curability, in addition to their tolerability to radiation better than adults.[12,13] Despite the low rate of relapses/recurrences, long-term follow-up is

recommended, as well as endocrine monitoring, due to iatrogenic hypothyroidism.[13] Optimum treatment in children has yet to be established, however, therapeutic strategies have been adapted from established treatment guides for adults, and the core treatment for pediatric, non-metastatic nasopharyngeal carcinoma is radiotherapy.[14,15]

CONCLUSION

Although exceedingly rare, we should consider NPC in the differential diagnosis of palpable neck masses especially in recurrent cases with no improvement after adequate medicamentosa. A multidisciplinary team approach in the diagnosis, and treatment is an uppermost importance. Another important point to be considered in diagnosing NPC in children is to think outside the box and do not expect any typical symptoms. Evaluation of complication from the extension of the mass should be considered in pediatric case of nasopharyngeal carcinoma.

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