Case Report

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Uncommon presentation of a huge intrathoracic ganglioneuroma in an 8-year-old child: a rare case report

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Abstract

Ganglioneuroma (GN) is a rare benign neurogenic tumor which arises from the neural crest cells that represent the final maturation stage of neuroblasts. GN is commonly encountered in adolescent or young adult. Until now, only a few cases of intrathoracic GN were reported in pediatric patients, especially in below 10 years of age. We report here an 8-year-old boy, who first presented to primary care with symptoms of upper respiratory tract infection. Radiologic investigations revealed a giant posterior mediastinal mass extending from T4 to T9 vertebrae without evidence of vascular invasion or infiltration into adjacent structures. The patient subsequently underwent left thoracotomy and resection of mass under general anesthesia. He was discharged 3 days after operation without complication. Histopathologic examination confirmed the diagnosis of thoracic GN. Grades of the neuroblastic differentiation increase with the median age at diagnosis. Although GNs are usually benign, they can grow aggressively and cause compression to an adjacent structure. Therefore, surgical resection is the only treatment. Debulking of tumor provides an alternative solution, especially when vital structures are involved. Complete resection remains the gold standard treatment for GN. However, in cases of incomplete resection, all residual tumors require regular clinical and radiodiagnostic follow-up.

Keywords: Ganglioneuroma, Posterior mediastinal mass, Neurogenic tumor

Background

Ganglioneuroma (GN) is a rare benign neurogenic tumor formed by neural crest cells that represent the final stage of maturation of neuroblast tumors[1]. Most GNs are thought to develop de novo rather than by maturation of existing neuroblastoma[2]. GN is classified under tumor of the peripheral autonomic nervous system arising from neural crest cells, including the sympathetic ganglia and the adrenal glands. Other examples of tumor arising from neural crest cells include peripheral nerve sheath tumors, melanomas, and neuroendocrine tumors[3]. It is a rare tumor, commonly encountered in adolescents older than 10 years of age or young adults[4]. To date, only few cases of giant intrathoracic GNs were reported in pediatric patients, especially in below 10 years of age. Peripheral nerve sheath tumors represent a spectrum of diseases from undifferentiated and malignant neuroblastoma to well-differentiated and benign GN. On the basis of the classification of International Neuroblastoma Pathology (the Shimada System), neuroblastic tumors are classified into 4 groups: neuroblastoma (schwannian stroma-poor); GN intermixed ganglioneuroblastoma nodular (GNB) or ganglioneuroblastoma intermixed (GNBI) (schwannian stroma-rich); nodular GNB or GNBN (schwannian stroma-rich/stroma-dominant and stroma-poor); GN (schwannian stroma-dominant), which is further divided into 2 subtypes (maturing and mature)[5]. The majority (73.5%) of nerve sheath tumors were found in adults[6] and solitary GNs occur slightly more often in girls than boys, with a female-to-male ratio of about 3:1[7]. GNs can be found in the posterior mediastinum (40%), but they are more commonly retroperitoneal and adrenal in origin[8]. Hampson et al[9], on the other hand, reported an uncommon finding of GN in the middle mediastinum in an elderly woman. Hence, neurogenic tumors should be considered in the differential diagnosis of a middle mediastinal mass. They may arise anywhere along the paravertebral sympathetic plexus and only a small proportion (1%–6%) of GN is

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of adrenal origin and most commonly occurs in children and young adults[10,11]. GNs have also been reported to occur rarely in other locations, such as the tongue, bladder, uterus, bone, and skin[11]. Almofada et al[12] reported an extremely rare case of GN involving the external auditory canal and middle ear, who presented with recurrent ear discharge and hearing impairment. Usually, patients with GN do not have symptoms of the disease due to the absence of hormone secretion[13] but few patients exhibit hypertension and hot flushes due to hypersecretion of catecholamines[2,14].

GNs are commonly benign but can grow aggressively and cause compression. Tumor extension into one of the hemithorax is common. Occasionally, there is an invasion into adjacent structures in the mediastinum. Mediastinal GN, especially in children occupying a large portion of a hemithorax, which may occur respiratory distress[1]. Hayat and colleagues reported that a lady with GN had almost occupied the entire left hemithorax, and it was covered with mediastinal pleura, adherent to the chest wall, pulmonary hilum and descending aorta, but did not invade any of these structures[6]. Some reports suggested that so far there are no characteristic findings of computed tomography (CT) or magnetic resonance imaging (MRI) in GN that help to distinguish it from other pathologies[15]. A recent study has shown that posterior mediastinal tumors with a broad base along the anterolateral aspect of the spine are more likely to be GN rather than schwannoma or neurofibroma[16].

Thoracic GN shows hypodensity in plain CT. On CT scan and MRI, nonenhancement or slight enhancements in the artery phase and progressive mild enhancement in the delay phase are characteristic manifestations of GN in the thorax with occasional intratumoral deposits of punctuating calcified materials[17,18].

MRI of the thorax is necessary to identify the possible extension of the tumor into the spinal canal. MRI features of GN include homogenous to heterogenous low signal intensity on T1-weighted images (T1WI), and heterogenous high signal intensity on T2WI[18]. The role of positron emission tomography (PET) scan as part of the preoperative assessment is uncertain. To date, little is known about the investigations of PET-CT in GN. PET scan was used as part of the assessment for the case of fat-containing GN. The presence of intratumoral fat and increased 18F-2-fluoro-2-deoxyglucose uptake suggests low-grade malignant potential[19]. The cut-off value of SUVmax was taken to be 1.8, which is believed to be the optimal value to distinguish benign neurogenic tumors from malignant neoplasms such as malignant peripheral nerve sheath tumor[2]. When both CT and MRI are unable to distinguish GN from other tumors, to obtain a definitive diagnosis, the histopathologic examination is necessary[13]. Fine-needle aspiration cytology is an excellent tool which can be used to differentiate benign from the malignant mediastinal lesion.

Histologic classification of GN should have a schwannian stroma-dominant maturing histology based on the histologic classification published in a large series of cases[3]. If cytology reveals both spindle and mature ganglion cells in smears, a diagnosis of GN is made[20]. The absence of immature cells (mitosis/karyorrhexis) and necrosis or inflammation differentiates GNs from their malignant counterparts, for example, GNB[21]. In the context, it is important to achieve a correct diagnosis technique for the detection of neuroblastic tumors owing to the prognostic and therapeutic implications.

Fat-containing GNs have a mixture of mature adipocytes (a mixture of white and brown adipose tissues in peripheral areas), spindle-shaped cells and fibrotic stroma but rarely reported in the literature[19]. The pathogenesis of fat-containing GNs may be due to the replacement of atrophied tumor lesions by mature adipose tissues or metaplasia or degenerative changes[22]. Immunocytochemistry of S100-positive spindle cells can also help to establish the neurogenic origin of the tumor cells[19].

Case report

An 8-year-old boy, with a medical history of beta-thalassemia, presented with his guardian to primary care with symptoms of upper respiratory tract infection. He had otherwise no history of shortness of breath or constitutional symptoms. His clinical examinations were unremarkable except for reduced air entry over the left middle zone. A chest x-ray was performed at a primary care clinic, which showed a large mass occupying most of his left hemithorax (**Fig. 1A**).

He subsequently underwent contrast-enhanced CT of the thorax and revealed a large heterogenous enhancing lesion measuring $6.3 \times 7.3 \times 8.9$ cm (antero-posterior × width × craniocaudal) at the posterior mediastinum extending from T4 to T9 vertebrae, occupying about 40% of his left hemithorax (**Fig. 1B**). There were multiple calcified foci, septations, and fluid attenuation within. The mass was abutting the adjacent descending aorta, left pulmonary artery and left segmental bronchus but there was no evidence of vascular or airway invasion. MRI confirmed no extension into the spinal canal or neural foramina (**Figs. 2A, B**). Laboratory blood tests were also within normal ranges.

Ultrasonography-guided fine-needle aspiration and cytology were performed a week after contrast-enhanced CT thorax, and histopathologic examination showed a strip of tissue composed of neoplastic ganglion cells arranged in nests with surrounding interlacing fascicles of spindle cells resembling Schwann cells, and keeping with GN. There was no neuroblastoma component identified in this biopsy.

The patient was electively admitted for preoperative assessment. Two days later, he underwent left posterolateral thoracotomy at the level fifth intercostal space under general anesthesia. Intraoperatively, a large mass was found to attach to the posterior chest wall. Extrapleural dissection was performed to ensure good clearance margin.

The mass was removed en bloc with the capsule intact and sent for histopathologic examination. Macroscopically, the tumor comprises of nodular cystic brownish tissue measuring $100 \times 80 \times 80$ mm. The nodular cystic lesion is covered by the smooth and glistening surface on one side and irregular surface at another side (**Figs. 3A, B**). Cut sections of the nodular lesion show multiple cystic lesions, which measure a diameter between 5 and 45 mm containing greenish gelatinous material.

Microscopically, the lesions show a well-circumscribed and encapsulated tumor composed of scattered clusters of mature ganglion cells exhibiting eccentrically located nuclei, prominent nucleoli, dense eosinophilic granular cytoplasm, and distinct cytoplasmic membrane (**Fig. 3C**). Area of myxoid change with cystic degeneration and hemorrhage is noted (**Fig. 3D**). The surrounding stroma is composed of abundant bland spindle Schwann cells (**Figs. 3E, F**). There were neither immature components found nor Homer Wright rosette and cellular atypia or mitotic figure. No evidence of malignancy was observed. The resection margins were clear of tumor both in macroscopically

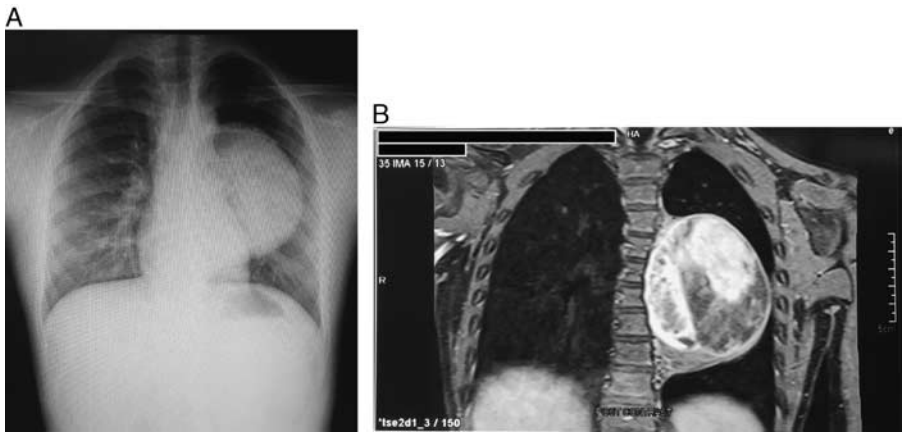

Figure 1. A, Chest x-ray shows large homogenous mass occupying almost half of the left hemithorax. B, Contrast-enhanced computed tomography of the thorax and revealed a large heterogenous enhancing lesion, extending from T4 to T9 vertebrae.

and microscopically. Immunocytochemical staining showed S100 protein positivity, which confirmed the diagnosis of GN.

The patient recovered well postoperatively without any complications and discharged home on the third day of postoperative surgery.

The patient underwent CT scan surveillance first in 3 months, followed by 6 months and 1 year after the surgery. There were no signs of recurrence, and the patient remained disease free after 1-year postresection of thoracic GN.

Discussion

GN and the variants are commonly found in adolescents older than 10 years of age or young adult as compared with those with immature neuroblastoma[4]. Some authors observed that the grade of neuroblastic differentiation increases with the median age at diagnosis[2,3]. Staging of the tumor is done according to the International Neuroblastoma Pathology Classification (INPC)[3,23]. Although GNs are commonly benign as compared with other

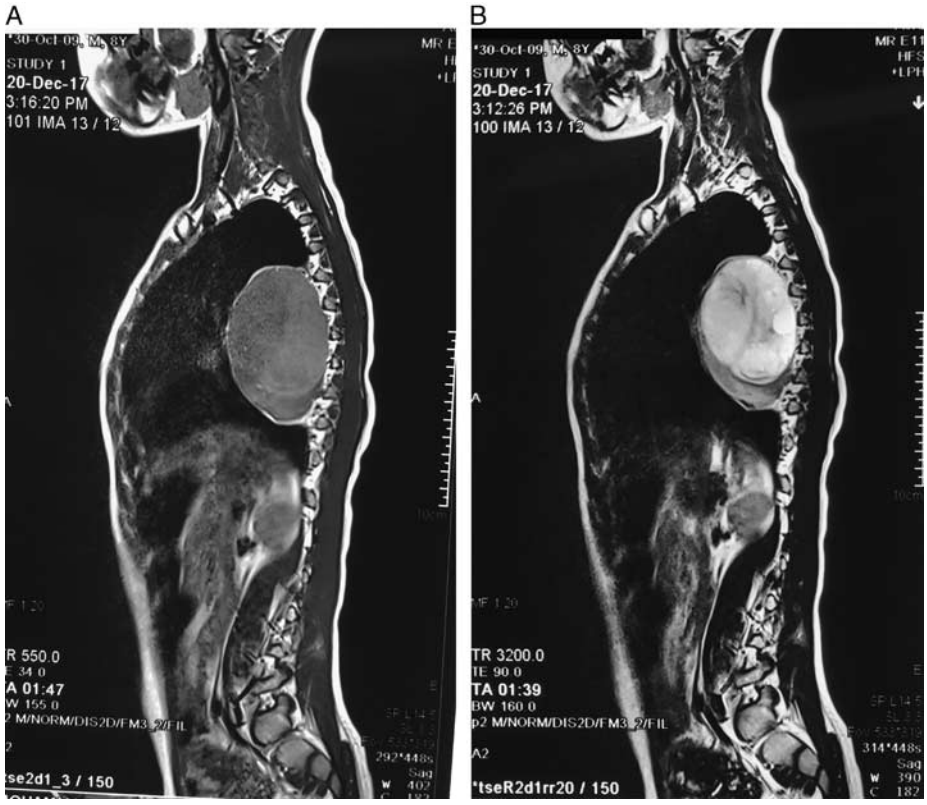

Figure 2. A, Magnetic resonance imaging of thorax (T1-weighted image) shows heterogenous low signal intensity. B, T2-weighted image shows a heterogenous hyperintense lesion with multiple septations within. No evidence of extension showed into the spinal canal or neural foramina.

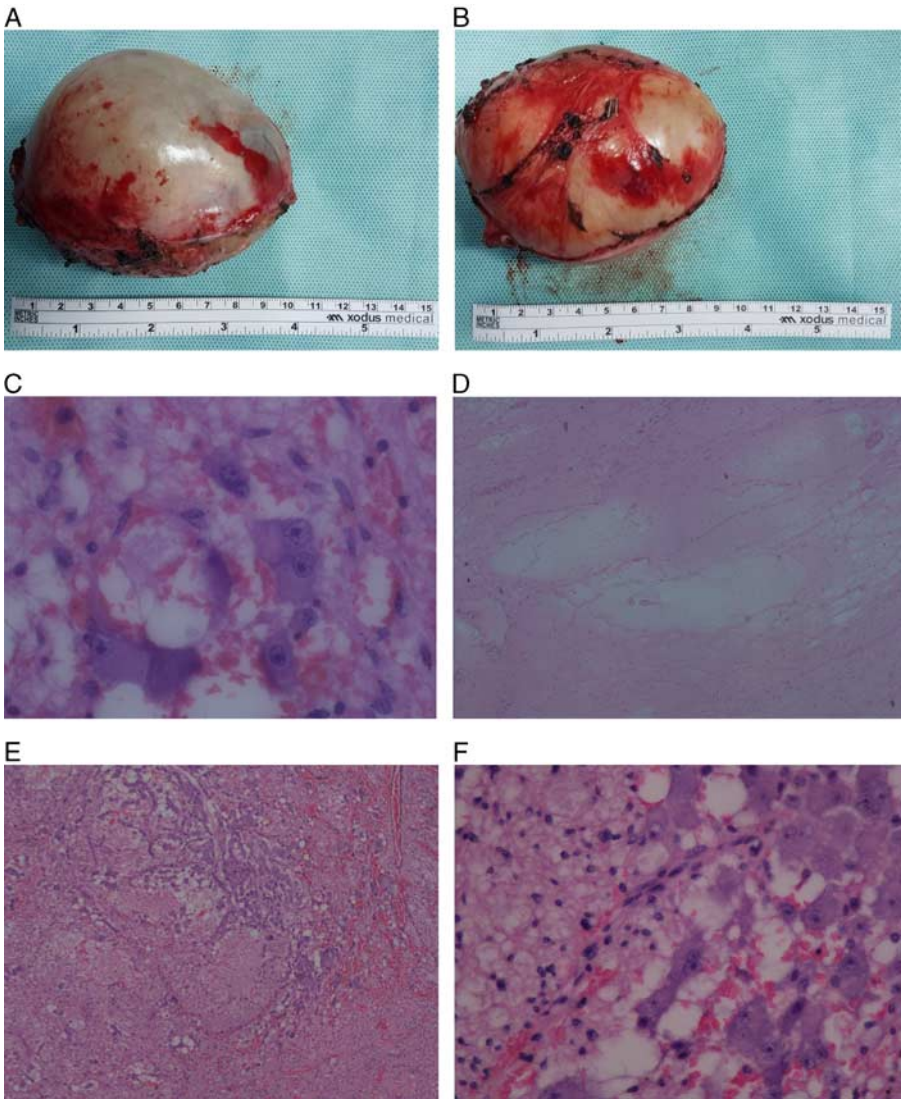

Figure 3. A and B, Gross specimen of an encapsulated tumor with the smooth and glistening surface on one side and irregular surface at another side. C, Scattered clusters of mature ganglion cells exhibiting eccentrically located nuclei, prominent nucleoli, dense eosinophilic granular cytoplasm, and distinct cytoplasmic membrane (hematoxylin & eosin, ×600). D, Myxoid background with an area of cystic degeneration (×40). E and F, Clusters of ganglion cells in the background of fibrillary neuronal stroma characteristic of schwannoma stroma (×40, ×400).

subtypes of mature neuroblastic tumors such as GNBN or GNBI, but they can grow aggressively and cause compression to adjacent structure. GNBI is widely seen as a malignant entity and treated with multimodal therapy[23,24]. Possible differential diagnoses include schwannoma, benign neurofibroma, malignant peripheral nerve sheath tumor or immature neuroblastoma. The clinical manifestation and radiologic findings may be similar, and the final diagnosis can only be confirmed via histopathologic examination and immunocytochemical staining.

The role of measurement of serum or urine catecholamines remains uncertain. Geoerger et al[2] showed and analyzed the metabolic and clinical featured of GN and demonstrated that a relevant proportion of GN shows (metaiodobenzylguanidine) mIBG uptake and elevated catecholamine metabolites in urine. Nevertheless, unlike neuroblastoma, most GNs are hormonally silent. Approximately, up to 30% of patients were found to have elevated plasma and urinary catecholamine, but they rarely develop symptoms of vasoactive amines excess[5]. GN showed less often positive mIBG-uptake and elevated urine catecholamine metabolites than GNBI and other types of immature neuroblastoma[23].

So far there is no medical treatment for GN, and complete surgical resection remains the mainstay of treatment. Patients treated surgically for benign neurogenic tumor have an excellent prognosis[24].

Complete resection of the lesion should be recommended and multisectioning of the whole specimen must be performed, paying particular attention for small foci of hemorrhage or necrosis, in order to confirm the diagnosis of GNB[21]. Besides, incomplete resection of GN is not associated with increased risk of progression if tumor residuals are smaller than 2 cm[23]. Hence, the resection does not have to be radical for the treatment of GN. Instead, subtotal resection without endangering vital structures seems to be sufficient[25]. In addition, GNBN or GNBI requires more intense multimodal treatment depending on the tumor stage and molecular markers[23]. Progressions only occurred in tumor

residuals that were larger than 2 cm in diameter[23]. Literature showed that most patients remained disease free for 2–3 years after surgical removal[6,19].

In conclusion, for a patient with GN, tumor resection without any cytotoxic treatment is recommended while complete resection is still widely recommended as the standard treatment for GN. Evidence suggested that incomplete resection in cases of adherent tumors (with minor residuals <2 cm), might be sufficient for the treatment of GN with regular examination of residual tumors via imaging.

Ethical approval

This case report has been registered under Malaysian Research Ethic Committee (MREC) and National Institutes of Health (NIH) Ministry of Health, Malaysia for publication.

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Author contribution

C.S.K. did the literature search and wrote the report. T.S.C. and L.J.C. both prepared the case summary. S.K. and S.Y.S. both performed the Surgery (resection of tumor). M.B.M.D. carried out the histopathologic examination of the sample. S.Y.S. and Y.H.J. both supervised the project.

Conflict of interest disclosure

The authors declare that they have no financial conflict of interest with regard to the content of this report.

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