

Retroperitoneal ganglioneuroblastoma with postoperative stress ulcer perforation in an adolescent: A case report and review of the literature

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Received January 29, 2022; Accepted May 3, 2022

DOI: 10.3892/ol.2022.13329

Abstract. Ganglioneuroblastoma (GNB) is a condition belonging to the neuroblastoma family. It is a transitional tumor consisting of a mixture of mature ganglioneuromas and malignant neuroblastomas. Its biological behavior is intermediate between benign and malignant, with a risk of recurrence and metastasis. It usually occurs in pediatric patients aged <10 years, particularly between the ages of 1 and 2 years, but may also occur in adolescents or adults. The present study reported on the clinical management of a case of postoperative stress ulcer with perforation in a 17-year-old female patient with retroperitoneal GNB and provided a review of the literature on retroperitoneal GNB in adolescents and adults.

Introduction

Ganglioneuroblastoma (GNB) is an embryonal tumor originating from primitive neural crest cells in the neuroectoderm (1). It is a transitional tumor consisting of a mixture of mature ganglioneuromas (GNs) and malignant neuroblastomas (NBs), hence its biological behavior is intermediate between that of GN and NB. Furthermore, GNB is a malignant or potentially malignant tumor (1,2). It usually occurs in pediatric patients aged <10 years, particularly between the ages of 1 and 2 years (3). By contrast, GNB is rare in adolescents and adults, with previous studies reporting <50 cases in adults (4). The most common site of origin for GNB is the adrenal medulla (~35%), followed by the retroperitoneum, brain and mediastinum, with tissues such as the orbit and parotid gland

also reportedly involved (5-13). Although cases of GNB in adolescents or adults have been previously reported, GNB occurring in the retroperitoneum is rare. The present study reported on a case of retroperitoneal GNB in a 17-year-old female who had an abdominal computed tomography (CT) finding of an occupying lesion in the head of the pancreas and underwent retroperitoneal tumor resection, which was confirmed by pathology to be GNB. On the third day after surgery, the patient developed a stress duodenal ulcer perforation and underwent an emergency major distal gastrectomy and duodenal ulcer resection. The present study reviewed the clinical course of this case together with an analysis and discussion of relevant literature.

Case report

A 17-year-old woman was admitted to the Affiliated Hospital of Guizhou Medical University (Guiyang, China) on September 7, 2021, for a whole abdomen CT scan at 9 days post-trauma that revealed a pancreatic head mass. However, the patient had no symptoms of nausea, vomiting, acid reflux or abdominal pain. Furthermore, no mass was palpated on examination and no positive signs such as abdominal tenderness, rebound pain or abdominal muscle tension were present. The patient had a previous gastroscopy diagnosis of a peptic ulcer (no gastroscopy report was available) and a history of prolonged and intermittent non-steroidal drug (NSAID) use for menstrual pain. The patient had a previous artificial abortion but no medical history of hypertension, diabetes mellitus, hepatitis or tuberculosis. However, the patient had a cystic solid occupancy in the posterior pancreatic head with clear borders ~120x64 mm in size as per the color Doppler ultrasound and enhanced CT of the abdomen; furthermore, the nature and origin of the tumor required further examination (Fig. 1). Magnetic resonance cholangiopancreatography (MRCP) revealed a morphologically irregular abnormal mass shadow behind the right posterior pancreatic head in the peritoneal area (~62x52x125 mm) with a non-uniform signal and well-defined borders; the enhancement scan indicated that the mass was not significantly strengthened (Fig. 2). After admission, laboratory tests for routine blood, liver and renal function, as well as coagulation and tumor markers were all unremarkable. The preliminary diagnosis was a retroperitoneal occupancy

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Key words: ganglioneuroblastoma, retroperitoneal, stress ulcer, adolescent, case report

neurogenic tumor. The patient then underwent exploratory laparotomy and retroperitoneal mass resection under general anesthesia on the 8th day post-admission. The operation went well and the patient returned safely to the ward after surgery and was given basic treatment, such as pantoprazole sodium for acid suppression and gastric protection and fluid supplementation. Based on the intraoperative findings (Fig. 3A-C), the mass was located in the right retroperitoneum of the hepatoduodenal ligament, was ~12 cm in diameter, soft with a complete capsule, movable and well defined. The mass was closely associated with the surrounding nodal tissue, posterior aspect of the head of the pancreas, portal veins, superior mesenteric veins and pancreatic hooks, but no distant metastases or enlarged lymph nodes were observed, as no images other than those of the tumor were acquired. During the surgery, the tumor was completely removed and the abdominal cavity was closed after careful examination and confirmation that no lesions remained and no adjacent organs or blood vessels were damaged. The tumor was irregular in shape, measuring ~13x7x5 cm, was solid, grey-white, soft, and had yellowish-white streaks on the cut surface. Microscopic observation revealed scattered, thread-like and nested tumor cells with sheets of necrosis. Certain cells had abundant cytoplasm and were eosinophilic, various cells had displaced nuclei with clear, vesicular nucleoli; certain cells had a nodular distribution with nests of immature small cells within the nodules and deeply stained heterogeneous nucleoli, and multinucleated cells and nuclear divisions were also observed (Fig. 3D and E). The immunohistochemistry results were as follows: Vimentin(+), S100(+), Sox10(+), CD56(+), CD57(+), specific esterase (SE) (+), neurofilament (NF)(+), synaptophysin (Syn)(+), friend leukemia integration-1(+), glial fibrillary acidic protein (less +), CgA (less +), myogenin (partial +), myogenic differentiation 1 (partial +), CD99 (partial +), smooth muscle actin(-), desmin (-), caldesmon (-) and Ki-67 (average of ~2%; hotspots of ~10%+) (Figs. 3F and G and S1). The pathological results were consistent with the diagnosis of retroperitoneal GNB.

On the third day after surgery, the patient presented with abdominal distension, abdominal pain and palpitations. Physical examination revealed significant whole abdominal pressure, rebound pain and abdominal muscle tension. Emergency blood cell analysis revealed a white blood cell count of $22.41 \times 10^9/l$ and neutrophil percentage of 90.50%. Abdominal CT indicated pneumoperitoneum, exudate and effusion in the abdominal cavity and pelvis, as well as edema in the gastric sinus and duodenal wall (Fig. 4). Stress ulcers with peptic perforation were considered in the context of the patient's physical signs, laboratory tests and abdominal CT results. An emergency laparotomy was performed on the 4th day after the first surgery, which revealed a thick accumulation of pus in the original surgical area and a perforation in the posterior wall of the duodenal bulb ~3.0x2.0 cm, with intestinal fluid spillage. After obtaining informed consent from the patient's family, the patient underwent major distal gastrectomy and duodenal ulcer resection. The pathological results indicated old duodenal ulcers with inflammatory exudation, granulation and fibrous tissue hyperplasia, scar formation and ulcerative changes in the plasma membrane of the intestinal canal (Fig. 5).

The patient recovered well from the second surgery and was discharged in good condition, with no recurrence or metastatic tendencies noted at the follow-up examination.



Figure 1. Contrast-enhanced computed tomography demonstrated progressive and modest enhancement of the lesion. (A) Arterial phase, (B) venous phase and (C) late phase. The mass was located between the posterior aspect of the head of the pancreas and the right kidney. The lesion was in close contact with the portal vein but no signs of infiltration were present. Lymphatic involvement or distant metastases were not observed (the white arrow indicates the position of the tumor).

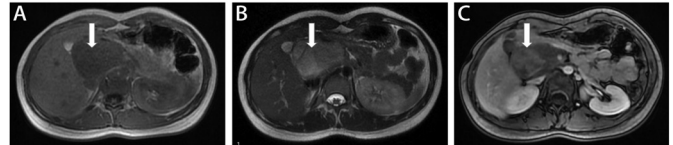


Figure 2. Magnetic resonance cholangiopancreatography confirmed the anatomic relationships of the mass as seen on computed tomography. (A) On T1-weighted imaging, it predominantly exhibited a slightly low signal, whereas in (B) T2-weighted images and T2-fat suppression images, it predominantly exhibited a slightly high signal, with a small amount of plaque-like slightly low signals and separated shadows. (C) After contrast medium injection, it was characterized by a progressive, heterogeneous contrast enhancement (the white arrow indicates the position of the tumor).

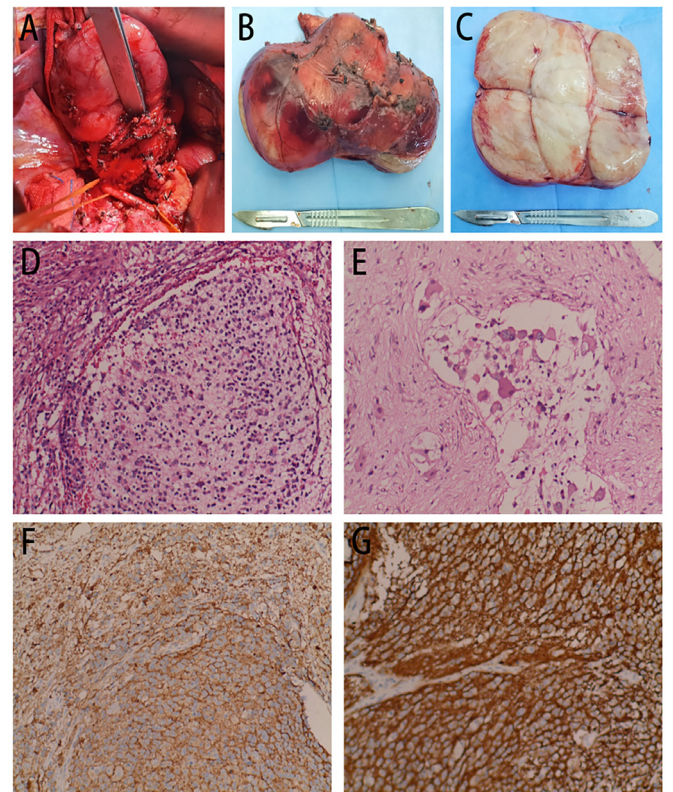


Figure 3. (A) Intraoperative image; the mass was located in the right retroperitoneum of the hepatoduodenal ligament with a complete capsule. (B and C) Gross images of resected mass. (B) The tumor was irregular in shape, measuring ~13x7x5 cm; (C) It was solid, grey-white and soft, with yellowish-white streaks on the cut surface (scalpel length ~15 cm). (D and E) H&E staining indicated that the percentage of neuroblastoma cells was significantly higher than that of mature ganglion cells and nerve fibers. Magnification, (D) x100 and (E) x40. (F and G) Immunohistochemistry indicated (F) Syn(+) and (G) CD56(+) (magnification, x100).

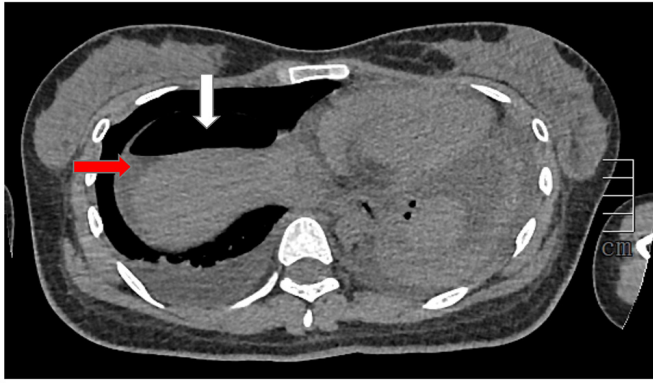


Figure 4. Abdominal unenhanced computed tomography confirmed the presence of pneumoperitoneum (white arrow) and effusion (red arrow).

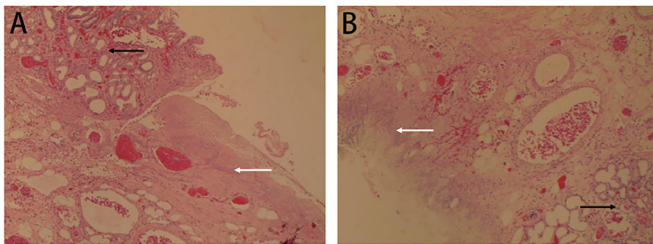


Figure 5. (A and B) H&E staining confirmed the presence of inflammatory exudate (white arrows) and hyperplasia (black arrows) of granulation and fibrous tissue in the duodenal specimen (magnification, x40).

Discussion

In 1947, Stout reported the first case of a tumor consisting of a malignant NB nodule and a mature GN, which was termed a mixed peripheral NB (14). In 1984, Shimada *et al* (15) summarized 295 cases of NB tumors and first introduced the concept of GNB; GNBs were then classified as nodular or mixed. In 1999, the International Classification of Neuroblastoma Pathology adopted Shimada's classification and revised it in 2003, redefining neuroblastoma and classifying it into NB, mixed GNB, GN and nodular GNB according to histological features (16,17).

As part of the present study, the PubMed database was searched using the subject key terms 'ganglioneuroblastoma', 'GNB', 'retroperitoneum' and 'retroperitoneal' (January 27, 2022). A total of 330 papers with titles containing GNB were found, of which only 14 (4.24%) were related to the retroperitoneum (12,13,18-29). Among these papers, there were 59 cases involving retroperitoneal GNB, and of these, 53 (89.8%) cases were in children (<12 years), one (1.7%) was in an adolescent (12-20 years) and five (8.5%) were in adults (>20 years). Thus, retroperitoneal GNB in adults or adolescents is rare. The present study reported the clinical course of another case of retroperitoneal GNB in a 17-year-old female and summarized the data on non-pediatric cases (age, >12 years) of GNB as follows (Table I).

The clinical symptoms and signs of GNB and NB are similar; however, the degree of malignancy and prognosis exhibit a great variation. CT and MRI are the most commonly used imaging methods to differentiate GNB from NB. A

previous study has also indicated that on CT, NB is mostly located in the adrenal region, with vascular inclusions, local infiltration, organ and lymph node metastases, and clustered or linear dilated vascular shadows around and within the tumor. However, GNB tumors frequently display a regular shape with well-defined margins and are accompanied by pressure displacement of surrounding large vessels (18). Due to the diversity of GNB components and the heterogeneous distribution of the fibrovascular network (which in turn may undergo bleeding and necrosis), the majority of CT enhancements are heterogeneous (18,30). GNB exhibits equal or slightly low signals on MRI T1WI, whereas T2WI is dominated by heterogeneous slightly high signals and the necrotic area exhibits longer T2 signals. The signal level of T2WI reflects the proportion of parenchymal cells and stroma in the tumor to a certain extent and the slightly low signal is dominated by parenchymal cells (31). In the present case, no significant changes were observed on the enhanced CT in the arterial phase, with mild enhancement in the venous and delayed phases, whereas the pancreatic ducts and portal veins were displaced by compression. The MRCP exhibited a predominantly slightly low signal on the T1WI image and a predominantly slightly high signal on the T2WI and T2-FS images, with a small amount of plaque-like slightly low signals and separated shadows. Although CT and MRI are useful in the diagnosis of GNB, the diagnosis of the disease is still dependent on pathological examination of the tumor tissue. The diagnosis is usually confirmed by microscopic findings of NB components and mature ganglion cells, frequently with nuclear schwannoma, hemorrhage, necrosis and calcification. In addition, Syn, CD56, SE, NF, CgA and S100 may be considered as GNB-specific markers (32).

Early radical surgery is the best treatment for retroperitoneal GNB and its prognosis is related to the ratio of neuroblasts to ganglion cells. If there are fewer neuroblasts, the patient's prognosis is better; conversely, if there are more neuroblasts, the patient's prognosis is worse as well. In addition, patient age and tumor size are also associated with GNB prognosis. Previous studies have indicated that patient age is inversely related to prognosis of GNB, with older pediatric patients having worse prognoses than younger pediatric patients (33-35). Furthermore, adults with GNBs >8 cm in diameter are frequently at risk of distant metastases (36). Compared to other reports of retroperitoneal GNB lesions, the present case had a larger lesion size (13 cm), hence the risk of recurrence may be increased. Therefore, GNB lesions in adolescents or adults should be carefully followed up, even after complete resection.

Stress ulcers are acute mucosal erosions and ulcers of the gastrointestinal tract that occur in stressful conditions such as shock, trauma, critical illness or surgery (37). The incidence of stress ulcers has significantly decreased with the widespread use of proton pump inhibitors (38-40). In the case of the present study, the patient developed abdominal pain and elevated body temperature on the third postoperative day, and laboratory tests and imaging data confirmed a peptic ulcer with perforation. Review of the surgical procedure did not indicate any injury to adjacent organs or blood vessels. Combined with the patient's previous history of peptic ulcer and history of NSAID use, the possibility of stress ulcer with

Table I. Information on previously reported non-pediatric cases of ganglioneuroblastoma and the present case.

First author/s, year	Country	Patient age, years	Sex	Symptoms	Therapy	Diagnostic basis	Comorbidity	Outcome	(Refs.)
Marya and Gupta, 1979	India	14	Male	Abdominal distension and pain	Surgery	H&E	-	Improvement	(25)
Yamanaka <i>et al</i> , 2001	Japan	60	Male	Back pain	Surgery	H&E+IHC (NSE, S100)	-	Died	(13)
Hayama <i>et al</i> , 2012	Japan	55	Female	Abdominal pain	Surgery	H&E+IHC (S100, NF, Syn)	Mature cystic teratoma	Improvement	(21)
Jrebi <i>et al</i> , 2014	USA	33	Male	Back pain	Surgery + chemotherapy	H&E	-	Died	(19)
Chen <i>et al</i> , 2014	UK	21	Female	Back pain	Surgery	H&E	Pregnancy	Improvement	(20)
Present study	China	17	Female	-	Surgery	H&E+IHC (Vim, S100, CD56, CD57, SE, NF, Syn)	Stress ulcers	Improvement	

H&E, hematoxylin & eosin; IHC, immunohistochemistry; NSE, neuron-specific enolase; NF, neurofilament; Syn, synaptophysin; Vim, vimentin; SE, specific esterase.

perforation was considered. As the patient's pathological examination results indicated GNB with malignant tendency and the ulcer perforation area was large (3.0x2.0 cm), it was difficult to achieve the ideal treatment result with the conventional ulcer repair surgery and the final decision was made to perform 'major distal gastrectomy and duodenal ulcer resection'. Therefore, active and effective prevention of stress ulcers has an important role in saving the patient's life as well as improving the patient's quality of life.

Controversy still exists as to whether patients with GNB should be treated with chemotherapy after surgery. The main chemotherapeutic agents used in pediatric patients include cyclophosphamide, vincristine, adriamycin and etoposide. Raina *et al* (41) reported a case wherein complete remission was achieved with a combination of cyclophosphamide, vincristine, adriamycin, cisplatin, etoposide and ifosfamide. In addition, certain studies have demonstrated that neoadjuvant chemotherapy is effective in patients with GNB (33,41-44), but its prognostic impact remains uncertain due to the low incidence of GNB. The pathological results of the patient of the present study suggested a high proportion of NB and a poorly located tumor with a close relationship to the surrounding tissues. After multi-disciplinary treatment discussion, chemotherapy or classical meta-iodobenzylguanidine treatment was recommended, but the patient and her family decided not to proceed with chemotherapy for the time being.

Recurrence of the disease mainly occurs 2 years after surgery. Patients should therefore be followed up for a long period and reviewed every 6 months, which should include a full blood count and imaging of the primary tumor site (45).

In conclusion, GNB is a transitional tumor frequently occurring in children. It consists of a mature GN and malignant NB and is therefore malignant or potentially malignant. to date, <50 adult or adolescent cases have been previously reported and there are only five cases of retroperitoneal GNB in adults or adolescents in the PubMed database.

Although the diagnosis of GNB depends on histopathological analysis, imaging with CT and MRI may still aid in GNB diagnosis. When an abdominal mass is found in an adult or adolescent, clinicians should consider the possibility of GNB and its malignancy and proactively prevent the development of complications.

Acknowledgements

Not applicable.

Funding

The present study was supported by the Special Fund for Outstanding Young Scientific and Technological Talents of Guizhou Province [grant no. (2019)5647] and the Science and Technology Fund Project of Guizhou Health and Family Planning Commission (grant no. gzwjkj2020-1-101).

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

SLZ and BLX examined the patient, analyzed the clinical, radiological and laboratory results, and wrote the manuscript. YWZ assisted with data analysis. XYF and ZHZ were involved in the surgical treatment. SZ designed the study, including proofreading of the manuscript and revising it critically. SLZ, BLX, YWZ, XYF, ZHZ and SZ confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient and their family for the publication of this case.

Competing interests

The authors declare that they have no competing interests.

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