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Ganglioneuroblastoma of the Nodular Variant in an Adult Female: Diagnostic and Treatment Dilemmas

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Abstract

Ganglioneuroblastoma (GNB) is a common pediatric cancer but rarely presents in adults. We describe a case of a 25-year-old woman who was diagnosed with GNB nodular (GNBn) after presenting with severe back pain. Our patient underwent a gross total resection and is currently under observation with no further treatment. Available treatment options are discussed in the case of recurrence.

Keywords: Ganglioneuroblastoma; Nodular variant; Neuroblastoma in adults

Introduction

Neuroblastomas are heterogeneous tumors with a potential for varied differentiation and can spontaneously regress, become malignant, or act benign [1]. They derive from neural crest cells [2] and therefore can develop into any organ in the sympathetic nervous system [3]. Neuroblastic tumors are most commonly found in pediatric patients, and when they are diagnosed in adults, they are classified as high-risk tumors associated with a poor prognosis [4].

Neuroblastic tumors can present in three ways, from least differentiated to most highly differentiated: neuroblastoma (NB), ganglioneuroblastoma (GNB), and ganglioneuroma (GN) [5]. The patient in this case study presented with GNB, a rare tumor that occurs almost exclusively in children. Roughly 650 cases in the United States are reported annually, 50% of which occur in children under the age of 2, and 75-85% of which occur in children under the age of 4 [6]. While it is one of the common pediatric cancers, fewer than 50 cases of adult GNB have been reported [7]. Prognosis in adults depends on the extent of resection, with gross total resections (R0) having the most favorable outcome [8].

Though malignant, GNB is less aggressive than NB, and consists of small, round, immature neuroblast cells and mature ganglion cells [9]. GNB can be further divided into two subtypes, including intermixed and nodular [10]. Intermixed GNBs consist of microscopic nests of neuroblastoma situated in a ganglioneuromatous stroma [7]. Nodular GNBs contain gross nodules-immature small cells-of neuroblastoma situated in large expanses of ganglioneuroma-big, mature cells in a fusiform stroma [7]. Our patient presented with GNB, nodular (GNBn).

Case Presentation

A 25 year-old female presented with severe right-sided back pain in March 2016. A CT scan from March 2016 revealed a right paraspinal mass with curvilinear calcifications depicted in (Figure 1). She was sent for an MRI, which revealed a heterogeneous enhancement with three nodular components. Several differential diagnoses were initially considered, including plexiform schwannoma, sarcoma, and metastasis. The diagnosis was confirmed upon core-needle biopsy of the right paraspinal soft tissue, which revealed a biphasic mass as shown in (Figure 2). One component consisted of bland spindle cells and a few admixed cells with features of ganglion cells. The second component was composed of atypical epithelioid cells with increased mitotic activity, focal rhabdoid cells, and multinucleated cells. Immunohistochemistry (IHC) revealed findings consistent

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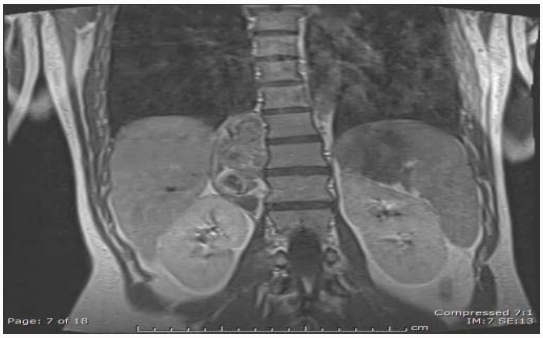

Figure 1: Coronal T2 MRI image demonstrates 3 nodular components on the right lumbar spinal region with mixed T2 signal.

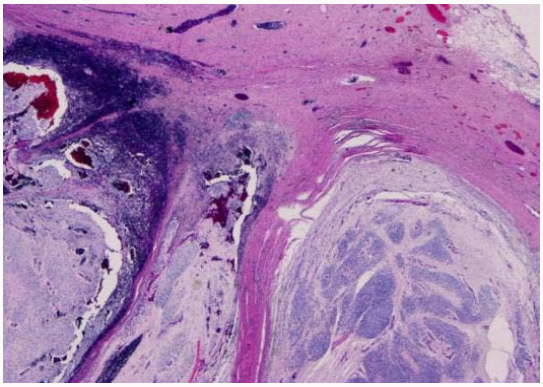

Figure 2: Biphasic appearance consisting of well-circumscribed hypercellular nodules in a background of hypocellular stroma.

with ganglioneuroblastoma (GNB), highly likely the nodular variant (GNBn) (Figure 3 and 4). The tissue was negative for MYCN gene amplification, suggesting a less aggressive tumor and better prognosis for the patient [11].

Prior to surgery, the patient was sent for an MIBG scan, an imaging test commonly used in lieu of PET to confirm up take of radioisotopes by foci of neuroendocrine tumor cells. A gross total resection of the spinal tumor with neurosurgery and thoracic surgery was performed in April 2016. Tumor margins were negative. Tissue was sent to Foundation One for next-generation genetic sequencing, which revealed an ALK point mutation at R1275Q. ALK encodes a receptor tyrosine kinase (RTK) that is part of the insulin receptor super family and induces downstream activation of pathways associated with cell survival, angiogenesis, and proliferation [12]. ALK mutations in neuroblastoma are associated with increased ALK protein expression and shorter survival [13-15]. After gross total resection, observation alone was decided for the patient. Currently, she is stable and receiving no radiation or chemotherapy, as her imagery findings continue to show no residual cancer.

Discussion

We present a case of nodular GNB in a 25-year-old female to highlight some of the difficulties in recommending treatment for this type of tumor. GNB is a rare disease that almost exclusively affects pediatric population; fewer than 50 cases have been reported in adults. In all cases, the treatment of choice was radical resection [9]. According to one study, every adult patient whose tumor was only partially resected or not resected died within 24 months [16].

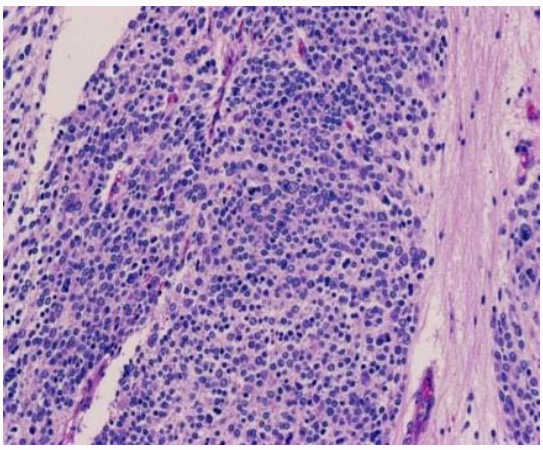

Figure 3: Higher power image of nodules. Consist of blue cells with high nuclear/cytoplasmic ratio, fine chromatin, and low mitotic/karyorrhectic index.

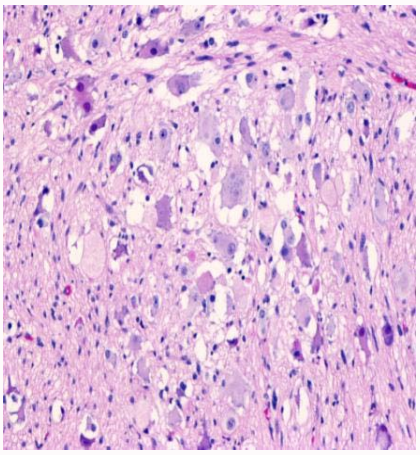

Figure 4: High power image of hypocellular areas show bland spindle cells with admixed ganglion cells.

Recurrence has been found to occur most frequently within the first two years after surgery [9]. Therefore, evidence supports the high importance of close clinical follow up, as well as imaging including CT scan and MIBG scintigraphy every 6 months, within the first two years after surgery [16]. Additionally, patients with GNBn have been found to have a high risk for distant metastases [17].

As for chemotherapy options, given that there have only been a few cases of adult GNB to set treatment precedence, we looked to pediatric cases for guidance. Active chemotherapeutic agents currently in use for pediatric population include cyclophosphamide vincristine, adriamycin, and combinations with platinum and etoposide. In the event of recurrence, topotecan [18] and temozolomide [19] have been demonstrated effective in the pediatric population. Additional drugs have been suggested based on the patient's particular genetic alterations. Crizotinib is an inhibitor of MET, ALK, RO1, and RON kinases and is FDA-approved to treat patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are positive for ALK or ROS1 rearrangements [20]. Similarly, ceritinib inhibits ALK, ROS1, IR, and IGF-IR kinases and is approved for patients with NSCLC in patients whose tumors are positive for ALK rearrangements and who are intolerant to crizotinib [20-23]. Alectinib is another option that has been approved for NSCLC for patients who have progressed or are intolerant to crizotinib [20].

Conclusion

The current study provides additional evidence for the importance of a gross total resection in treatment of GNB in adults. Additionally, this case study presents several treatment options based on pediatric precedents and the patient's unique genetics. Close post-operative follow up increases the chance for early detection in the cases of recurrence and higher chance for survival.

Consent

The patient has consented to the use of their health information for research purposes.

Conflict of Interest

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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