Clinical Case Report

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Orbital neuroblastoma metastasis

A case report and literature review

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Abstract

Rationale: Neuroblastoma is one of the most common tumors found in children, and mostly arises in the adrenal gland and paravertebral regions. Orbital neuroblastoma metastasis is relatively rare, and is associated with poor prognosis. Since the symptoms and signs of orbital neuroblastoma are not specific, its diagnosis remains challenging.

Patient concerns: A 3-year-old girl presented with periorbital ecchymoses (raccoon eyes) and proptosis for 40 days.

Diagnosis: Abdominal magnetic resonance imaging (MRI) and sonography analysis revealed a large mass in the left adrenal gland (primary tumor). The computed tomography and MRI further revealed multiple soft tissue masses in the skull and both orbits with erosion of the adjacent bones (the metastasis). The histological analysis of the tumor removed from the right orbit confirmed the diagnosis of neuroblastoma.

Interventions: The mass on the right face was surgically removed.

Outcomes: The patient exhibited no deteriorative signs at the 6-month follow-up.

Lessons: Clinical manifestations, such as periorbital ecchymoses and proptosis, in combination with radiological analysis and histological findings, are important for the diagnosis of orbital neuroblastoma metastasis.

Abbreviations: CT = computed tomography, FFA = fundus fluorescein angiography, H&E staining = Hematoxylin-eosin staining, MRI = magnetic resonance imaging, NSE = neuron-specific enolase, OCT = macular optical coherence tomography, SYN = synaptophysin, TH = tyrosine hydroxylase.

Keywords: adrenal tumor, case report, neuroblastoma, orbital metastasis

1. Introduction

Neuroblastomas are the most frequently identified extracranial tumors that affect children under the age of 4 years old, with an incidence of approximately 1 to 3 in 100,000 cases.[1,2] These account for approximately 6% to 10% of all pediatric tumors and 15% of tumor-related deaths in children.[3] Neuroblastomas are neuroendocrine tumors that can originate anywhere in the sympathetic nervous system, although these are most commonly found in one of the adrenal glands. The clinical symptoms and signs of neuroblastomas are commonly atypical, depending on the location of the primary tumor and metastases. Although metastasis to the orbits has been well-documented for neuroblastomas presenting with various symptoms, such as periorbital ecchymoses (raccoon eyes) and proptosis,[4] neuroblastoma cases with initial symptoms of orbital involvement are rare, accounting for approximately 8% of all neuroblastomas.[5] In the present study, we report a specific case of a 3-year-old girl with neuroblastoma, who presented with initial signs of periorbital ecchymoses (raccoon eyes) and proptosis. In addition, the clinical, radiological, and histopathological studies of orbital neuroblastoma metastasis reported in the literature were summarized.

2. Case presentation

The present study was approved by the Ethics Committee of the Central Hospital of Wuhan, Tongji Medical College of Huazhong University of Science and Technology. All procedures performed in studies that involved human participants were in accordance with the ethical standards of the institutional and national research committee, and the 1964 Helsinki declaration and its later amendments, or comparable ethical standards. A written informed consent was obtained from the patient's legal guardian.

A 3-year-old girl was admitted to our hospital presenting with periorbital ecchymoses and proptosis for 40 days. On examination, multiple hard masses were palpated on both the face and

Editor: N/A.

W-JY and Y-YZ authors have contributed equally to this work.

A written informed consent was obtained from the patient's legal guardian for the publication of this case.

This work was supported by the National Natural Science Foundation of China (No. 81300761) and the Research Projects of Wuhan Health and Family Planning Commission (WX18A08, and WX17Z02).

The authors have no conflicts of interest to disclose.

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How to cite this article: Yang WJ, Zhou YY, Zhao F, Mei ZM, Li S, Xiang Y. Orbital neuroblastoma metastasis. Medicine 2019;98:36(e17038).

Received: 15 January 2019 / Received in final form: 15 July 2019 / Accepted: 12 August 2019

http://dx.doi.org/10.1097/MD.0000000000017038

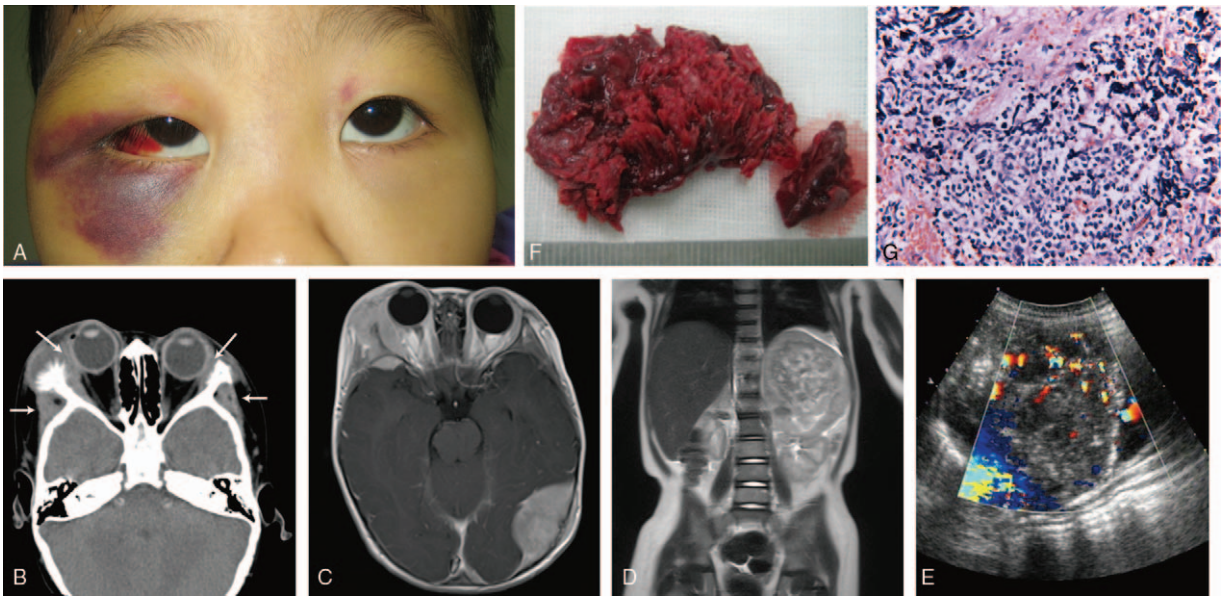

Figure 1. The lesion, radiological findings, and histological results of the 3-year-old girl with orbital neuroblastoma. (A) A photograph of the lesion showing the subconjunctival hemorrhages, periorbital ecchymoses (raccoon eyes), and proptosis. (B) An axial CT scan showing the bilateral proptosis and subperiosteal masses intraorbitally (narrow arrows) in the sphenoidal walls. The tumor also extended to the temporal foss (arrows). (C) The craniocerebral MRI reveals multiple hypointense soft tissue masses in the head-face area of the T1-weighted images. (D) The abdominal MRI shows a large mass lesion in the left adrenal gland protruding into the upper-middle abdomen. (E) The longitudinal abdominal sonograph shows a heterogeneous, hypoechoic mass with hyperechoic areas, and increased vascularity in the left adrenal gland. (F) The tumor removed from the right face was lobulated and hemorrhagic. (G) The H&E staining revealed uniform small, round cells with a scanty cytoplasm and darkly stained nuclei (400× magnification). CT = computed tomography, H&E staining = Hematoxylin-eosin staining, MRI = magnetic resonance imaging.

head. Bilateral subconjunctival hemorrhages, periorbital ecchymoses (raccoon eyes), and proptosis were identified (Fig. 1A). Fundus fluorescein angiography (FFA) and macular optical coherence tomography (OCT) revealed no abnormality on the fundus. The systemic evaluations, which included routine blood and urine tests, hepatic and renal function examinations, and the serum glucose test, revealed unremarkable findings, with the exception of anemia. The electrocardiogram and chest roentgenogram results were also unremarkable. However, an abdominal mass was palpated by a pediatrician.

The computed tomography (CT) scan highlighted multiple soft tissue masses in the skull and both orbits, with evident erosion into the adjacent bones (Fig. 1B). The magnetic resonance imaging (MRI) also revealed multiple masses in the head-face area, and a large mass in the left suprarenal gland (Fig. 1C and D). The abdominal sonography examination revealed a heterogeneous hypoechoic mass in the left adrenal gland (Fig. 1E).

The mass on the right face was surgically removed. The tumor was cardinal red, with an irregular surface (Fig. 1F). The hematoxylin-eosin (H&E) staining revealed small uniform round cells with a scanty cytoplasm and darkly stained nuclei. Furthermore, nodules and Homer-Wright pseudorosettes were occasionally found, with no ganglionic differentiation (Fig. 1G). The tumor was immunopositive for synaptophysin and neuron-specific enolase, but immunonegative for S-100 and leukocyte common antigens. According to the clinical, radiological, and histopathological findings, the patient was diagnosed with stage IV neuroblastoma. The patient was transferred to the Department of Pediatric Oncology for the treatment of the tumor. However, the patient refused the recommended chemotherapy, which included cisplatin, doxorubicin, etoposide, and ifosfamide. Hence, the patient was discharged without any therapeutic regimen. The patient presented no deteriorative signs at the 6-month follow-up.

3. Discussion and conclusion

Orbital tumors in children can rapidly develop and lead to vision loss, and are associated with significant risk of mortality and morbidity.[6] Neuroblastoma is an undifferentiated malignant tumor that commonly occurs in children, which can rapidly metastasize and widely spread, resulting in a variety of clinical manifestations, such as proptosis, periorbital ecchymosis, abdominal pain, anemia, pancytopenia, bone pain, and paralysis.[7] In the present study, we present a case of a 3-year-old girl with stage IV neuroblastoma, who presented with periorbital ecchymoses and proptosis as initial symptoms. The diagnosis of neuroblastoma was confirmed by radiological analysis of the orbital tumors and an abdominal mass in the adrenal gland, as well as the characteristic histological findings of neuroblastoma. Since clinical manifestations and imaging features are not specific or defined for neuroblastoma, it remains difficult to differentiate neuroblastoma with orbital involvement from other metastatic orbital tumors, such as malignant lymphoma, rhabdomyosarcoma, granulocytic sarcoma, and Wilms tumors. Relevant literature was reviewed, and 10 cases of neuroblastoma with orbital involvement were found by searching PUBMED for published articles between 2000 and 2017 (Table 1). The clinical manifestations, radiological findings, and histological features of these cases, as well as the present case, were summarized (Table 1), which are integral to the clinical diagnosis and differential diagnosis of neuroblastoma with orbital involvement.

Periorbital ecchymoses and proptosis have been reported to be classic signs of pediatric neuroblastoma.[4,8] Consistent with

Table 1

Summary of cases of orbital neuroblastoma metastases.

Case	Author/publication year	Age/Gender	Symptoms and signs	Radiological findings	Histological findings	Diagnosis	Treatment	Clinical outcome
1	Cliff et al/2001[8]	26 months old/boy	Periorbital swelling, ecchymosis, subconjunctival hemorrhage, pancytopenia	Abdominal CT: aortocaval mass	Bone marrow: small round blue cell infiltration into the bone marrow cavity; Homer-Wright rosette formation	Stage IV neuroblastoma Primary site: Aortocaval region; metastasis site: widespread metastases to bone marrow	Chemotherapy (carboplatin, cyclophosphamide, vincristine, and cisplatin)	NA
2	Varma et al/2003[9]	2.5 years old/boy	Visual loss	Orbital CT: a large mass in the sphenoid region. Chest CT: a left paravertebral lesion in the thoracic area	Biopsied tissues: discohesive sheets of intermediate-sized cells with minimal cytoplasm and irregular nuclei	Stage IV neuroblastoma. Primary site: not identified; metastasis site: cervical and paratracheal lymph nodes and a left paravertebral lesion in the thoracic area; bone marrow.	Chemotherapy and high-dose retinoic acid	Symptoms improved at the 2-year follow-up
3	Bay et al/2005[5]	15 months old/boy	Periorbital ecchymoses, proptosis, abdominal pain, fever, vomiting	Abdominal CT: a left suprarenal mass	NA	Neuroblastoma primary site: supra-renal location metastasis: not reported	NA	NA
4	Gumus/2007[10]	10 months old/girl	Periorbital edema, ecchymosis proptosis	Abdominal CT: a left supra-renal mass	Bone marrow: Homer-Wright rosette formation	Stage IV neuroblastoma primary site: supra-renal location; Metastasis: widespread metastases to bone marrow	Local treatment	NA
5	Moran et al/2010[11]	1 year old/boy	Periorbital ecchymoses	Abdominal MRI: large right adrenal mass with hepatic metastases. Orbital MRI: bilateral periorbital metastatic infiltration with involvement of the meninges.	NA	Neuroblastoma primary site: not clearly, may be in the right adrenal gland; metastasis: hepatic, periorbital and meningeal metastasis	NA	NA
6	Salmi et al/2010[12]	20 months old/girl	Left orbital swelling	Orbital MRI: a left-sided mass in the sphenoid bone. Chest, abdomen, and pelvis CT scans did not reveal any other mass or lesion	Biopsied tissue: sheets of small, round, blue cells with high nucleus-to-cytoplasm ratio, fine immature chromatin, and inconspicuous nucleoli. Immunocytochemistry: neuron-specific enolase (+); tyrosine hydroxylase (+); desmin (–); CD45 (–); CD99 (–); chromogranin (–); S100 (–)	Stage IV neuroblastoma primary site: unknown; Metastasis: bone marrow	Chemotherapy (cisplatin, toposide, adriamycin, vincristine, cyclophosphamide, ifosamide) resection of the periorbital tumor local radiation, and autologous hematopoietic stem cell transplantation	Disease-free at last follow-up of 4 months
7	Muniz/2012[13]	21 months old/boy	Periorbital ecchymoses, proptosis, face swelling,	Orbital CT: extensive tumor invasion of the orbits and extensive bony erosions	Biopsied tissue: neuroblastoma	Neuroblastoma primary site: not reported. Metastasis: not reported	Chemotherapy	Died
8	Muniz/2012[13]	30 months old/boy	Periorbital ecchymoses, edema	Orbital CT: extensive tumor invasion of the orbits and extensive bony erosions. Abdominal CT: a mass	Biopsied tissue: neuroblastoma	Neuroblastoma Primary site: may be in abdominal cavity. Metastasis: not reported	Chemotherapy	Died
9	Ghosh et al/2012[14]	3 years old/boy	Periorbital ecchymoses, proptosis, vision loss, hepatosplenomegaly	Orbital CT: bilateral orbital metastasis and bony erosion. Abdominal CT: a large mass in the right adrenal gland	Biopsy from post-caval lymph node: metastatic deposits from neuroblastoma	Neuroblastoma Primary site: ma be in the right adrenal gland. Metastasis: bone marrow, post-caval lymph node, eye.	Chemotherapy (cisplatin, doxorubicin, etoposide, and ifosfamide) with other supportive measures	No evidence of recurrence within the follow-up period of six months; vision did not improve
10	Kurian et al./2016[15]	5 years old/boy	Proptosis, decreased supraduction	Orbital CT: an ill-defined lytic mass centered in the right zygoma with both intra- and extra-orbital extension	Bone marrow: sheets and nests of a small blue cell tumor infiltrating the bone marrow space with areas of hemorrhage and cystic formation	Neuroblastoma Primary site: paraspinal location Metastasis: diffuse metastasis	N/A	N/A
11	Present case	3 years old/girl	Periorbital ecchymoses, proptosis, subconjunctival hemorrhage, anemia	CT: multiple soft tissue masses in both orbits with bone erosion MRI: multiple masses in the head-face area. Abdominal MRI: a large mass in the left suprarenal gland. Abdominal sonography: hypoechoic mass in the adrenal gland	Biopsied tissue: small uniform round cells with scanty cytoplasm and darkly stained nuclei. Immunocytochemistry: Synaptophysin (+); NSE(+); S-100(–); leukocyte common antigen (–)	Stage IV neuroblastoma, primary site in the adrenal gland Metastasis: periorbital region	No treatment	Alive at the 6-month follow-up

CT = computed tomography, MRI = magnetic resonance imaging, NA = not applicable, NSE = neuron-specific enolase.

these symptoms, it was found that the most common clinical manifestation of neuroblastoma with orbital involvement reported in the literature was periorbital ecchymoses (8/11, 72.7%), followed by proptosis (6/11, 54.5%; Table 1). The emergence of periorbital ecchymoses is probably due to tumor obstruction of the blood vessels in and around the orbits. Less common ophthalmic manifestations include periorbital swelling/edema (5/11, 45.4%), subconjunctival hemorrhage (2/11, 18.2%), vision loss (2/11, 18.2%), and decreased ocular mobility (1/11, 9.1%). Other uncommon clinical associations include pancytopenia, anemia, abdominal pain, fever, vomiting, and hepatosplenomegaly, which may be associated with the metastasis of the tumor to the bone or other organs.

Since orbital neuroblastoma metastasis presents with nonspecific clinical manifestations, it is often misdiagnosed as child abuse, orbital fracture, or other tumors such as rhabdomyosarcoma. CT and MRI can provide valuable diagnostic information for neuroblastoma identification, especially for pin pointing the primary site of the tumor. A giant hypoechoic mass with hyperechoic areas is the most common abdominal sonographic finding,[16] which was observed in the present case. With the exception of case 11, abdominal CT and/or MRI scans were performed in all of the cases reviewed, and abdominal masses in the adrenal gland were often discovered. The radiographic findings in the orbits usually included thickened bones, periosteal reactions (speculated bones), and lytic defects. In the MRI scans, neuroblastomas usually present with heterogeneous low signal intensity on T1-weighted images and high signal intensity on T2-weighted images.[6]

The histopathological analyses of biopsied orbital masses were often performed to confirm the diagnosis of orbital neuroblastoma metastasis. The histological staining of the biopsied tissues revealed small round cells with a scanty cytoplasm and darkly stained nuclei.[9,12] Moreover, neural markers, such as neuron-specific enolase, TH, and synaptophysin, were often immunopositive in the tumor tissues, while S100 and leukocyte common antigens were immunonegative (Table 1).[12]

The present patient refused any therapeutic regimen. At present, the primary treatment for neuroblastoma is chemotherapy. Multiple protocols with various agents, including carboplatin, vincristine, etoposide,[8] cisplatin, doxorubicin, cyclophosphamide, and ifosfamide,[12] are presently available. Other combined therapeutic strategies include 13-cis-retinoic acid,[9] local radiation, resection of the periorbital tumor, and autologous hematopoietic stem cell transplantation. However, in case of more aggressive tumors, drug resistance should be resolved in the future. Targeting techniques by infusion of meta-iodobenzylguanidine conjugated to ^{131}I and ^{125}I are also promising for future developments.[17]

The prognosis for children with neuroblastoma is dependent on many factors, such as age at diagnosis, disease stage, and histological grade. Orbital neuroblastoma metastases are commonly associated with poor prognosis.[4] Among the 11 cases with orbital neuroblastoma metastases, systemic chemotherapy was initiated in 6 cases. Although the symptoms improved by follow up after 4 months to 2 years in 4 patients, 2 children died after chemotherapy. Furthermore, although the survival chances for children diagnosed with neuroblastoma have markedly improved over the last 30 years with the advance of multiple treatment modalities, such as chemotherapy, surgery, stem cell transplantation, and immunotherapy,[2] the survival rate for patients with neuroblastoma with orbital metastasis remains low.

Author contributions

Conceptualization: Wan-Ju Yang, Yuan-Yuan Zhou, Shuang Li, Yi Xiang.
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Writing – review & editing: Wan-Ju Yang, Yuan-Yuan Zhou, Fang Zhao, Zhong-Ming Mei, Shuang Li, Yi Xiang.

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