Extraskeletal osteosarcoma of the orbit: A clinicopathologic case report and review of literature

V M D S de Maeyer, P A F A Kestelyn, Akash D Shah[1], C M Van Den Broecke[2], H G N Denys[3], C E Decock

Primary extraskeletal osteosarcoma (EOS) is an extremely rare malignancy. In this report, the clinical course of a 32-year-old man presenting with proptoses is described. Medical history included Hirschsprung disease (HD), horseshoe kidney, azoospermia, and vertebral anomalies. Imaging of the orbit showed an oval, well-defined heterogeneous mass adjacent to the lateral wall of the orbit. The patient underwent a lateral orbitotomy and complete excision of the mass. The mass was not attached to the bone. Histopathologic and immunohistochemical examination confirmed the diagnosis of an EOS. The patient received chemotherapy and radiotherapy and is free of the disease 3 years after the diagnosis. Genetic screening showed no mutations for both the RET proto-oncogene for HD and the p53 tumor suppressor gene for osteosarcoma.

Key words: Extraskeletal osteosarcoma, Hirschsprung disease, p53 tumor suppressor gene, RET proto-oncogene

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Departments of Ophthalmology, [2]Pathology and [3]Medical Oncology, Ghent University Hospital, Ghent, Belgium, [1]Department of Orbit and Oculoplasty, Bombay City Eye Hospital, Mumbai, India

Correspondence to: Dr. V M D S de Maeyer, Department of Ophthalmology, Ghent University Hospital, De Pintelaan 185, 9000 Ghent, Belgium. E-mail: veroniquedemaeyer@yahoo.com

A 32-year-old man presented with an acute onset (3–4 weeks) proptosis of the left eye [Fig. 1a]. There was no history of other ocular complaints or trauma. Medical history included HD (stoma), horseshoe kidney, azoospermia, and vertebral anomalies.

Best-corrected visual acuity was 20/20 in both eyes. Examination of the left eye revealed an axial proptosis of 2 mm and minimal restriction of extraocular movements in all gazes. Fundoscopy of the left eye revealed minimal disc edema. Examination of the left eye was otherwise normal. Right eye examination was unremarkable.

Computed Tomography (CT) of the orbit showed an oval, heterogeneous, well-defined mass measuring 2 × 3.2 × 4 cm in the left orbit adjacent to the lateral orbital wall. The mass showed moderate contrast enhancement and large central calcifications [Fig. 1b]. There was bony remodeling with sparing of orbital structures. Magnetic resonance imaging (MRI) showed a mixed heterogeneous mass with hypo and hyperintense areas [Fig. 1c and d].

The patient underwent a lateral orbitotomy and complete excision of the mass using frozen section assessments. Intraoperatively, the tumor was not attached to the bone or to any of the orbital structures, and was excised completely with blunt dissection [Fig. 2a]. On gross examination, the tumor was

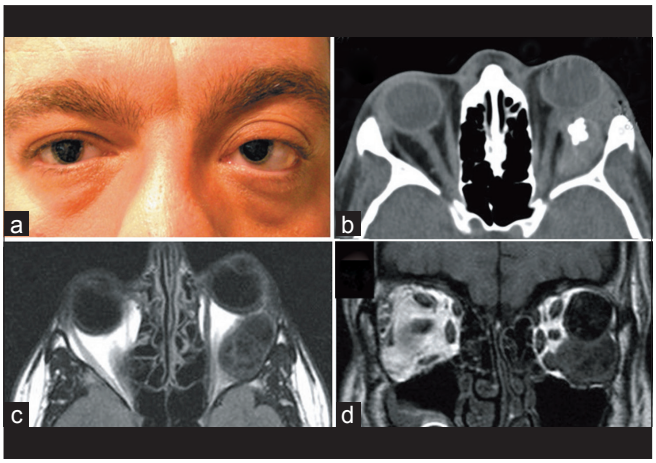

Figure 1: (a) Clinical photograph of the patient showing the axial proptosis in the left eye. (b) Computed tomography scan (axial view) of the orbit showing an oval, heterogeneous, well-defined mass measuring 2 × 3.2 × 4 cm, free lying in the left orbit near the lateral orbital wall with moderate contrast enhancement and large central calcifications. There was bony remodeling with sparing of orbital structures. (c and d) Magnetic resonance imaging of the orbit (coronal and axial) showing heterogeneous lesion with hypointense areas corresponding to the calcification and hyperintense areas corresponding to the tumor mass

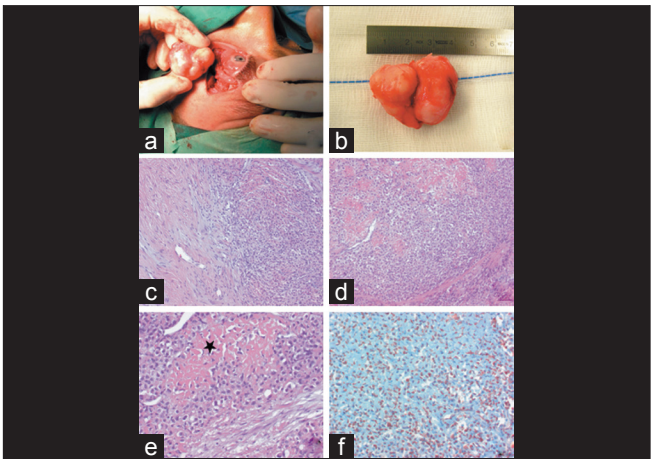

Figure 2: (a) Intra operative photograph showing complete excision of the mass from the orbit with no bony attachments, (b) Gross appearance of the excised tumor which was oval, well encapsulated, bilobed divided by a central sulcus measuring 3.1 cm × 2.3 cm × 3.2 cm, (c) Hematoxylin–eosin staining with low-power view showing the biphasic appearance of the tumor with cellular and acellular areas. The acellular areas consisted of dense fibrous areas (d), Low-power view of the cellular area showing osteoblast-like cells embedded in an osteoid matrix showing widespread, irregular foci of calcification, (e) High-power view of the cellular area showing cells with an epithelioid appearance and pleomorphic nuclei with foci of calcification (asterisk), (f) Immunohistochemical examination showing positivity of tumor cells to osteocalcin

bilobed, oval, well encapsulated, measuring 3.2 × 3.1 × 2.3 cm, with a calcified cut surface [Fig. 2b]. Microscopic examination revealed a heterogeneous lesion consisting of cellular areas intermixed with areas consisting mainly of dense fibrous tissue. The former consisted of osteoblast-like cells in an osteoid matrix that showed widespread, irregular foci of calcification. These cells had an epithelioid appearance, with pleomorphic nuclei [Fig. 2c, d and e]. Immunohistochemical examination was positive for osteocalcin and negative for actin, desmin, keratin, CD99, and S100 [Fig. 2f].

A systemic workup was carried out in the form of complete blood count, liver and renal function tests, whole body CT scan, and bone marrow biopsy, which revealed no evidence of the disease elsewhere. The patient was thus considered as having primary EOS of the orbit. Genetic screening was performed on chromosome 10q for *RET* proto-oncogene, the major susceptibility gene responsible for HD, and on chromosome 17 for p53 tumor suppressor gene responsible for osteosarcoma. However, no mutations were noted.

The patient was treated with six cycles of combination chemotherapy (cisplatin–adriamycin), followed by radiotherapy. In total, 70Gy was delivered through intensity-modulated arc therapy. On his last follow-up 4 years after diagnosis, the patient is alive without evidence of disease recurrence or systemic involvement.

Discussion

EOS is extremely rare and accounts for 2–4% of all osteosarcomas.[1] Patients with EOS usually present in the fourth and fifth decades of life unlike skeletal osteosarcoma patients who present in the fifth and sixth decades of life.[2] The extremities and girdles, especially lower, are most commonly involved.[1] There are also reports of EOS involving the face, breast, abdominal wall, soft tissues of the back and retroperitoneum, and site of a vaccination scar.[2-4]

Radiotherapy is known to predispose to the development of EOS. Sordillo *et al*. found that 10% of the patients had previous irradiation and 13% of the patients had history of trauma related to the site of EOS.[2] Our patient had no history of trauma or radiotherapy.

The genetic change most commonly associated with osteosarcoma is the loss of the p53 tumor suppressor gene on chromosome 17 and loss of retinoblastoma gene *RB1* on chromosome 13.[5] A genetic association between Paget's disease and osteosarcoma has also been identified on chromosome 18q.[6] Other genomic changes, such as loss on 13q and 15q and gain on 1q and 8q, have been detected in patients with EOS.[7] Medical history of the patient included HD. The contribution of the major susceptibility genes on chromosome 10q (*RET* proto-oncogene) is well established in HD.[8] In addition, potential modifying associations exist with chromosomes 2, 9, 13, 20, 21, and 22.[8] Variations of main *RET* proto-oncogene account for as much as 50% of familial and 20–30% of sporadic cases. The etiology of the majority of sporadic cases is not clear, appearing to arise from combined cumulative effects of susceptibility loci on other chromosomes controlling the mechanism of cell proliferation, differentiation, and maturation.[8]

A genetic association between HD and genitourinary abnormalities has been reported.[8] Presence of genitourinary abnormalities in the form of horse-shaped kidney and azoospermia, and sporadic HD pointed toward a genetic

abnormality in our patient. Hence, we performed genetic screening at the common sites for both HD and osteosarcoma on chromosome 10 (*RET* proto-oncogene) and chromosome 17 (p53 tumor suppressor gene). However, we found no abnormalities at both these loci, suggesting a role of combined cumulative effects of susceptibility genes on other chromosomes. Inactivation or alteration of a gene located at this susceptibility loci could have been an early event in the development of EOS in our patient.

Primary EOS has a very aggressive natural history. The cornerstone of treatment consists of radical surgery and polychemotherapy.[9] Due to the rare nature of this disease, no data from randomized studies concerning the type of chemotherapeutic combinations are available. In a small retrospective study, Goldstein-Jackson *et al*. reported favorable results when EOSs were treated as conventional osteosarcomas.[9] Active chemotherapeutic agents for skeletal osteosarcoma consist of a combination of doxorubicin and cisplatin, with or without the addition of other drugs such as methothrexate, ifosfamide, and etoposide. The use of multi-agent chemotherapy has extensively improved the outcome for skeletal osteosarcoma.[10] However, these treatments are very intensive, and therefore acute and delayed toxicities can be expected. Doxorubicin can cause bone marrow toxicity and cardiotoxicity, whereas cisplatin can cause nephro - and ototoxicity.[11]

Adjuvant radiotherapy does not increase the survival when patients are treated with effective surgery and chemotherapy, and increase the risk for secondary tumors.[12] However, radiation should be considered in the setting of an unresectable or incompletely resected primary tumor.[13] In this case, radiotherapy was delivered. The tumor was completely resected, but the resection margins were close due to the orbital localization of the tumor, making wide resection impossible.

To date, two cases of EOS involving the orbit have been reported. The first case was an 11-year-old boy who developed an EOS of the orbit following radiotherapy for retinoblastoma in infancy.[14] The second patient was a 22-year-old otherwise healthy male with no predisposing factor.[1] Our case is the oldest patient ever detected with an EOS in the orbit with no history of previous radiotherapy or trauma. One could suggest a possible association between EOS and patients known HD, but this has never been reported in the literature before.

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