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CASE REPORT

Osteosarcoma with Orbital Metastasis in a Nigerian Child: A Case Report and Review of the Literature

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Summary

Osteosarcoma is the most common primary bone tumour with a peak occurrence in adolescence. The occurrence of osteosarcoma in preadolescents is rare with a paucity of data in the developing world. Metastasis of osteosarcoma to the orbit is even a rarer presentation with few cases reported in the literature but to the best of the researchers' knowledge, none of the previous cases had contralateral orbital metastasis to osteosarcoma. This is the first case report of orbital metastasis of osteosarcoma in Nigeria. The present case is presented for its rarity, to increase awareness and add to knowledge on the possibility of metastasis to contralateral orbit in osteosarcoma.

Keywords: Bone malignancy, Childhood tumour, Osteosarcoma, Orbit, Neoplasm Metastasis, Nigeria.

Introduction

Osteosarcoma is the most common childhood primary bone cancer. [1] It is derived from primitive bone-forming mesenchyme. [2] It is a rare presentation in children with the peak age of occurrence in adolescents. [3] The annual incidence rate is 5.0/million in children below nineteen years. [4] It is commoner in males than females. [5]

Osteosarcoma occurs mostly in rapidly growing bones. This accounts for the peak occurrence in adolescence, a period of growth spurts. [1] The epiphyseal growth plates in the distal femur and proximal tibia contribute largely to height in puberty, hence it is a common site of affectation. [1]

The aetiology of osteosarcoma is largely unknown but the possibility of a viral origin has been suggested. [6] Other risk factors for osteosarcoma include exposure to ionizing radiation and chemicals such as asbestos and chromium salts. [7,8] Some of the chromosomal and genetic risk factors for osteosarcoma include hereditary retinoblastoma, Paget's disease, Bloom syndrome and Li-Fraumeni syndrome. [8-10] Like many other tumours, mutations in tumour suppressor genes like P53 and retinoblastoma (Rb) genes have been documented as causative factors for osteosarcoma. [1]

The most common clinical presentation of osteosarcoma is pain in the affected bone, [11,12] and the pain is typically worse at night and

occasionally related to mild trauma. [11] The commonly affected sites are the distal femur, proximal tibia and humerus. Rarely, the jaw, mandible, maxilla and vertebrae may also be affected. [4, 12] Swelling of the affected bones, limping gait and pathologic fractures are also commonly seen. [11] Fever, weight loss and night sweats are associated symptoms. [11] Metastasis to the lung, which is the commonest site of systemic metastasis, presents with pulmonary nodules. [13] Lung metastasis usually occurs within six months of treatment. Extra-pulmonary metastases are uncommon and mostly occur in the pelvis and vertebrae.

Orbital osteosarcoma is rare with few case reports. [15-18] The clinical presentation involves eye protrusion with associated pain, chemosis and loss of vision. With orbital metastasis, the absence of pulmonary metastasis occurs and this is due to the haematogenous spread of the disease through Batson's venous plexus. [14] The commonest primary disease site of previously reported cases is the tibia while the scapular was observed as a primary site in a case. [15-18] With careful search, there has been no previous report on orbital metastasis of osteosarcoma in Nigeria.

The investigations required to diagnose osteosarcoma include a plain radiograph that shows soft tissue mass, sclerotic and lytic lesions, sunburst appearance and Codman's triangle (wedge elevation of periosteum). [19] A chest radiograph and preferably, a chest computerized tomography, is required for the assessment of the lungs for pulmonary metastasis. [11,19] One of the biochemical markers in osteosarcoma is elevated alkaline phosphatase. It is also an effective prognosticating marker. [20]
The intraosseous and extraosseous extent of involvement, as well as skip lesions, are identifiable with computerized tomography (CT) or magnetic resonance imaging (MRI) scan. The proximity of the tumour to neurovascular structures can also be determined with MRI. The CT of the thorax is also helpful in establishing metastasis to the lungs. [11] Radionuclei bone scan can also be used in the diagnosis and staging of the tumour. This is useful in detecting metastasis to the bone. Positron Emission Tomography (PET) scan is useful in staging and monitoring progress during treatment. [21] Bone biopsy is an important definitive investigation required in making the diagnosis and staging of osteosarcoma. It characterises the tumour as either high or low grade. Histologic features include malignant cells producing osteoid calcification and atypical spindle cells. [22]

The management of osteosarcoma is multidisciplinary. It involves input from the paediatric oncologist, orthopaedic surgeon, radiologist and pathologist, as the modalities of treatment include chemotherapy, surgery and radiotherapy. [11] Chemotherapy, as a neo-adjuvant therapy before surgical intervention and post-surgery, is usually required. Commonly used chemotherapeutic agents include doxorubicin, cisplatin, ifosfamide and methotrexate. [11] Surgical intervention involves tumour resection, reconstruction and in some cases, amputation. [22,23] Radiotherapy is useful for local control of residual tumours following surgical interventions. [24]

The prognosis of childhood osteosarcoma depends on the stage of disease at presentation as metastasised tumours and incompletely resected tumours have guarded prognosis. [25] Skip lesions and poor response to neoadjuvant chemotherapy are poor prognosticating factors. [26] Orbital metastasis of osteosarcoma is rare and none have been documented with contralateral primary tumour site metastasis. This case report is to create awareness and further add to the knowledge of this rare form of metastasis.

Case Description

A 7-year-old girl presented at the Department of Paediatrics, Lagos State University Teaching

Hospital, Ikeja, Lagos, with right thigh and leg swelling of five months duration, left eye swelling of two months duration and weight loss. The lower limb swelling was preceded by pain and it progressively increased in size with associated inability to walk. The protrusion of the left eye was noticed three months after the swelling of the leg. The left eye swelling progressively increased in size, was associated with purulent bilateral eye discharge and subsequent loss of vision in the eye. The right eye was not affected.

There was progressive weight loss, evidenced by the loosening of previously fitted clothing, despite adequate food intake. Thereafter, there was a loss of appetite, occasional vomiting and generalized body weakness. She was initially taken to a traditional home where scarification marks were made on the legs in addition to herbal medications. At presentation in the hospital, she was cachectic, in painful distress, pale, afebrile and had no significant peripheral lymph node enlargement. There was a total loss of vision in the left eye. A fusiform swelling of the lower third of the right thigh and upper third of the leg was noticed [Figure 1(a)]. The swelling was bony hard with a shiny surface, warm to touch and tender. There were scarification marks with visible peripheral veins and preserved sensation distal to the swelling. The child also had a left-sided, fungating eye mass measuring 8cm by 10cm by 10cm; the eye had areas of necrosis with mucopurulent discharge and an oedematous eyelid and loss of vision [Figure 1(b)]. The initial clinical diagnosis was metastatic left retinoblastoma with probable right leg osteosarcoma.

The radiograph of the right lower limb showed a sunburst appearance around the middle and distal one-third of the right femur with lytic lesions in the proximal tibia and fibula [Figure 1(c)]. The chest radiograph showed no lung metastasis. Other investigations included tissue biopsy of the lower limb swelling, CT scan of the brain [Figures 1(d) and 1(e)], and some blood investigations as shown in Tables I and II. Histology sections of the right femoral bone showed malignant spindle to polygonal cells with peripheral spindling and central bone formation. They were seen producing osteoid deposits. Tumour giant cells and occasional mitosis were also identified. [Figures 1(f) and 1(g)] The diagnosis of periosteal osteosarcoma was made.

Following the histology of the leg swelling, chemotherapy was commenced: Doxorubicin (25mg/m^2), cisplatinum (100mg/m^2), ifosfamide (1.8g/m^2), etoposide (100mg/m^2) and carboplatin (400mg/m^2). She had four courses of chemotherapy (once in three weeks of chemotherapy) but the swellings progressively increased with more intense pain. Unfortunately, chemotherapy was discontinued due to financial constraint. However, left orbital exenteration was done and histology showed spindle-shaped cells infiltrating a fibromyxoid stroma in addition to single to multinucleated giant cells with hyperchromatic nuclei and areas of haemorrhage and osteoid deposits around the cells [Figure (f)]. Therefore, the diagnosis was revised to metastatic osteosarcoma of the right femur. The child received
several transfusions with blood and blood products, analgesics for pain, antibiotics and antifungal medications. Prevention of tumour lysis syndrome was achieved with xanthine oxidase inhibitor (allopurinol).
There was a response to therapy and palliative care with pain control but she died after fourteen weeks of admission from disease progression with an increase in both orbital and leg swelling and pancytopaenia.

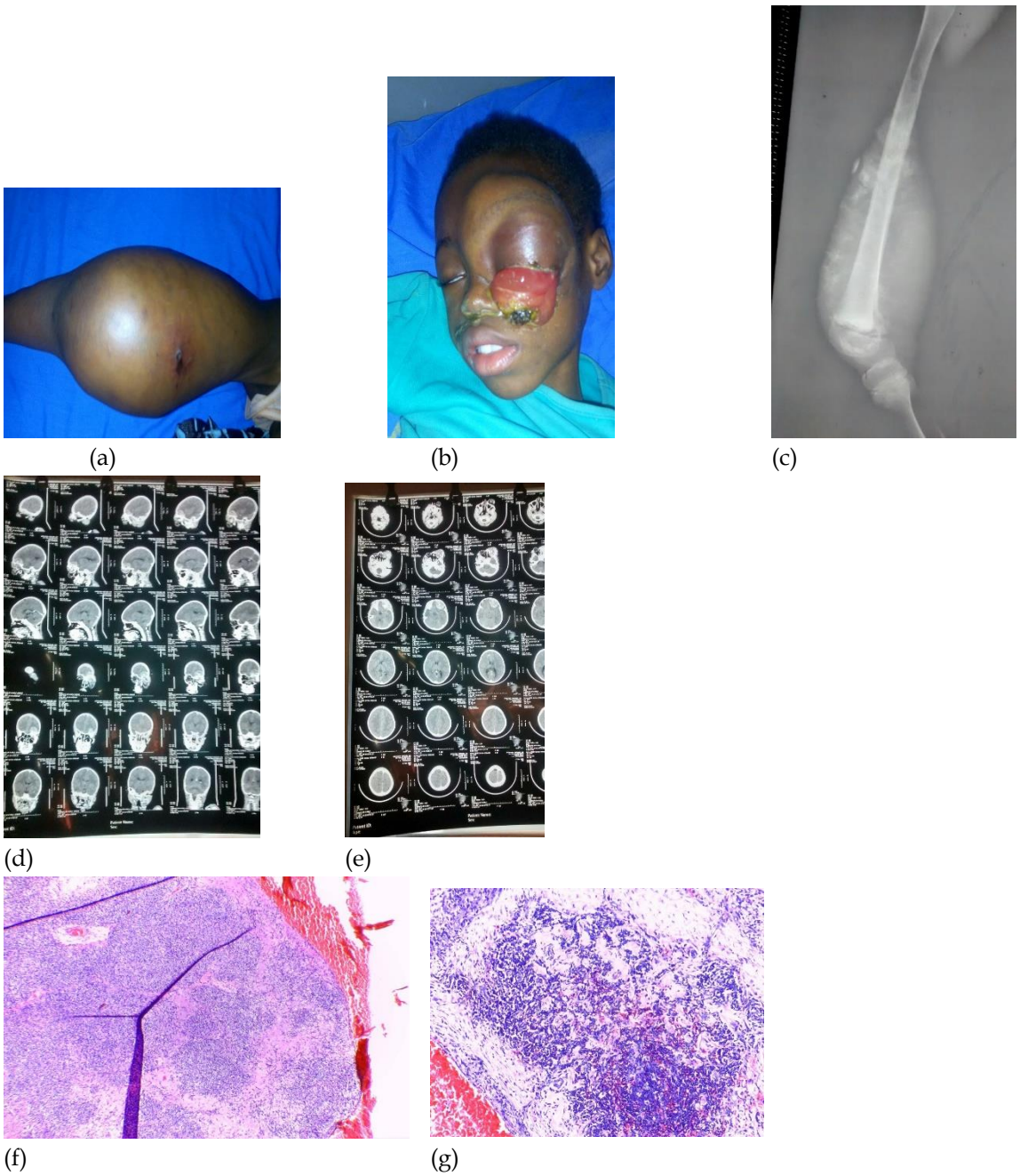

Figure 1: Clinico-pathological and radiological parameters of the child

Images: (a) Fusiform swelling of the lower third of the femur and upper third of the leg with visible veins and scarification. (b) Fungating left eye mass with areas of necrosis and mucopurulent discharge. (c) Sunburst radiographic appearance around the middle and distal one-third of the right femur with a lytic lesion in the proximal tibia and fibula. (d) & (e) Sagittal and Coronal skull MRI views showing the extent of the orbital mass. (f) Histology of left orbital mass showing spindle-shaped cells infiltrating a fibromyxoid stroma with single to multinucleated giant cells having hyperchromatic nuclei. Areas of haemorrhage and osteoid deposits around cells were also observed (g) Histology sections of the right femoral bone showing malignant spindle to polygonal cells with peripheral spindling, central bone formation, osteoid deposit production, tumour giant cells and occasional mitosis.

Table I: Serial full blood count profile

Full Blood Count	*24/12/2017*	*11/01/2018*	*08/02/2018*	*27/02/2018*
Haematocrit (%)	25	39.9	33.8	23.0
Total WBC (x 10^9 L)	0.81	2.95	7.8	0.2
Neutrophil (%)	6.8	60.2	68.7	83
Lymphocyte	91.4	12.2	24.4	9.8
Platelet Count (x10^9 L)	37	433	356	23

L = Litre; % = Percentage; mmol = Millimole

Table II: Serial serum biochemistry profile

Serum Biochemistry	*10/12/2017*	*08/12/2017*	*13/1/2018*	*16/01/2018*
Sodium (mmol/L)	136	127	136	136
Potassium (mmol/L)	2.2	3.0	6.1	7.0
Bicarbonate (mmol/L)	24	28	20	20
Chloride (mmol/L)	97	87	97	97
Urea (mg/dl)			35	35
Creatinine (µmol/L)			0.7	0.7
Serum Calcium (mmol/L)		1.71		

L = Litre; mmol = Millimole, mg/dl= milligram per decilitre

Discussion

Osteosarcoma is the most common malignant bone tumour but it is rarely seen in preadolescents. [1] Osteosarcoma has bimodal peaks of occurrence in ten to twenty-four years and adults above seventy years. [3] Its occurrence in adolescents has been linked to growth spurt at that period. [4] The rarity of osteosarcoma with case reports on subjects below ten years has been documented in parts of the world. In Nigeria, in a review of bone malignancies in an orthopaedic hospital, a case of osteosarcoma was reported in a seven-year-old child. [27] In addition, a higher occurrence of osteosarcoma in males has been previously documented.[4,27,28] This present case, however, occurred in a girl.

The index case presented at the hospital five months into the illness. The average duration before presentation documented in the literature is three to six months. [29] Late presentation of malignancies is very common in Nigeria and as illustrated in the index case, the delay could be traced to poverty and ignorance which led to seeking a cure from traditional practitioners. This is still a major challenge in Nigeria and other sub-Saharan Africa and a major contributor to the significant morbidity and mortality observed in childhood cancer in this sub-region.

The distal femur was the primary site in the present case with involvement of the proximal tibia, which are the actively growing parts of the bones, especially in adolescents. These sites are in keeping with documentation in the literature as the commonly affected sites. Osteosarcoma is commonly seen at the metaphyseal ends of long bones. [29] In 75% of femoral tumours, it affects the distal part, and 80% of tibia affectation is in the proximal region. [4] The first symptom in the index case was pain at the tumour site with subsequent obvious swelling in concordance with existing literature. [29] However, orbital metastasis of osteosarcoma as observed in the index case is rare. There are few reports from the middle eastern part of the world on orbital metastasis of osteosarcoma. [15-18] Some authors have

reported choroidal and eyelid metastasis. [30, 31] The rare presentation of this orbital metastasis contributed to the initial clinical misdiagnosis of this index case as retinoblastoma. This was subsequently considered unlikely because the eye mass was noticed after the swelling on the limb. More so, the presence of spindle cells and osteoid deposits on histology helped with the confirmation of the disease. Although osteosarcoma usually metastasizes to the lungs, no respiratory or radiograph abnormalities were recorded in the index case. Skip pulmonary metastasis occurs with orbital spread. This has been reported in cases earlier documented except one. [15,17,18,32] Non-pulmonary metastasis of osteosarcoma has been postulated to occur possibly through Batson's paravertebral system. [14] Surprisingly, to the best of these researchers' knowledge, contralateral left orbit metastasis secondary to right lower limb osteosarcoma, as observed in the index case, is not known in the literature. [15-18,32] Baston's plexus are valveless venous systems with bi-directional blood flow which perhaps may account for haematogenous metastasis to any orbit irrespective of the primary side. [14]

Chemotherapy as a neo-adjuvant to surgery is effective. This therapy was commenced in the index case and she was scheduled for surgery after twelve weeks of chemotherapy. However, there was no response to chemotherapy due to advanced disease stage at presentation as evidenced by progressive swelling of the eye and leg as well as pancytopaenia. The outcome of the disease is known to be poor when there is metastasis at the initial diagnosis and this was demonstrated in the index case. [33] Palliative radiotherapy could not be explored in the index case despite its beneficial effects in symptoms control, due to financial incapability and inaccessibility to that care. [34]

Poor knowledge of cancer and the overbearing traditional belief system, as seen in the index case, are factors that contributed to the adverse outcome in the index case. There is a need for increased dissemination of information on paediatric cancers, sources of appropriate care and need for prompt care-seeking. In addition, delay in laboratory investigation due to financial incapability and unavailability of blood and blood products may have contributed to the adverse outcome in the index case. The out-of-pocket health care financing system mostly practised in Nigeria impacts negatively on accessibility to quality health care. The high cost of investigations, chemotherapeutic medications and radiotherapy is a contributory factor to poor outcome and it calls for urgent attention.

Conclusion

Osteosarcoma in preadolescents is rare and metastasis to the orbit is yet rarer with only a few reports in the literature. There is a need for a higher index of clinical suspicion when children complain of pain on long bones and early institution of chemotherapy is desirable for better clinical outcomes.

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