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Blind Eye Associated with Osteosarcoma

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Authors' contributions

This work was carried out in collaboration between all authors. Author EPW is the main author and surgeon and wrote the first draft of the manuscript. Authors NE and GEO managed the analyses of the study including the histopathology. Author LA managed the literature searches. All authors read and approved the final manuscript.

Case Report

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ABSTRACT

We report the case of a 10 year old girl with a late diagnosis of a high grade osteosarcoma (Stage IIb) of the right femur in a low income setting. The diagnosis could clinically have been made much earlier if the observation of an enucleated congenitally blind left eye due to a probable retinoblastoma was known to be associated with osteosarcoma. Screening of at-risk families and close surveillance of affected individuals for these heritable genetic predisposition syndromes may permit earlier diagnosis and more effective treatment of osteosarcoma in these populations.

Keywords: Osteosarcoma; retinoblastoma; staging; treatment.

1. INTRODUCTION

There are many human cancers for which a hereditary predisposition plays a key role in tumour development. Retinoblastoma is the most common intraocular tumour in childhood and osteosarcoma is the most common primary bone tumour that affects both children and adults. The retinoblatoma (Rb) gene is responsible for the development of both retinoblastoma and osteosarcoma as structural deletions with one or both retinoblastoma gene alleles are commonly noticed in retinoblastomas and osteosarcomas [1]. Typically patients with the heritable form of retinoblastoma form a tumour in both eyes whereas the

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non heritable patients typically form a tumour in just one eye. Survivors of the heritable form of retinoblastoma subsequently may develop a second malignancy such as osteosarcoma at substantially greater frequency than either the general population or survivals of non-heritable retinoblastoma. The cumulative risk of second malignancies in retinoblastoma patients is 32%. Ninety-eight percent of second malignancies occur in patients with bilateral retinoblastoma [2] About 15% of those children with tumour in only one eye have the hereditary form of retinoblastoma and can pass the gene to their children and are greatly at an increased risk to develop second neoplasms particularly osteosarcoma. [2,3] In this case the time lapse was 10 years.

2. CASE PRESENTATION

A 10 - year old girl was admitted as an emergency with a fungating /ulcerating tumour of the right lower thigh. This was associated with persistent pain, weight loss, anaemia and fever. The painful swelling in the thigh was noticed two months previously following a minor collision with a bench- the minor injury drawing attention to the bone tumour. She was managed traditionally with massage and splinting but there was obviously no amelioration. She was then admitted to the local hospital where she was found to be anaemic. She was transfused a unit of blood and referred to a tertiary hospital. Her family preferred to attend a private orthopaedic clinic where she was further transfused 4 units of blood and a surgical exploration macroscopically revealed osteosarcoma. The patient refused amputation and the family refused oncological treatment not being convinced of the diagnosis. The wound dehisced 1 week later followed by the rapid growth of a fungating, ulcerating tumour. She was admitted to the Regional hospital for confirmation of the diagnosis and further advice on appropriate management. In the past at age 3, she had an enucleation of a congenitally blind left eye but there was no histopathological report (Fig. 1).

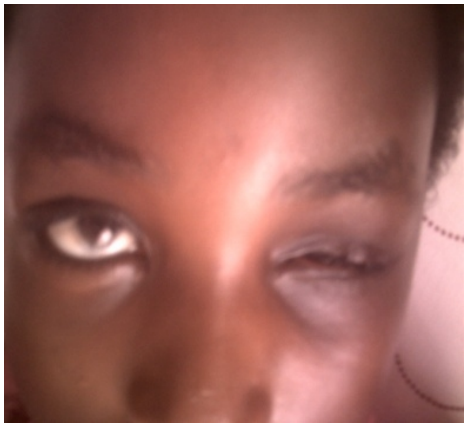

Fig. 1. Left enucleated eye due to probable non-heriditary retinoblastoma (with permission)

On examination she was very pale, cachetic, lethargic, irritable and in distress from constant pain. Apart from a tachycardia, the vital signs were normal. She had an enucleated left eye (closed eye-lid). There was a large 'ball-like' immobile, fungating tumour (~7cm d) on the medial aspect of the lower right thigh extending to the knee and ulcerating into skin (Fig. 2). It was hot with dilated superficial veins and an induration of the surrounding skin extending to the groin with vulvar oedema. There was purulent discharge from the ulceration and

tender palpable right inguinal lymphadenopathy. The right leg was swollen with a pitting oedema. Peripheral pulses were normal but there was a limited range of movement of the knee and hip joints due to pain and deformity. Apart from mild peripheral oedema, the left leg appeared normal. There was no clinical evidence of chest or abdominal metastases.

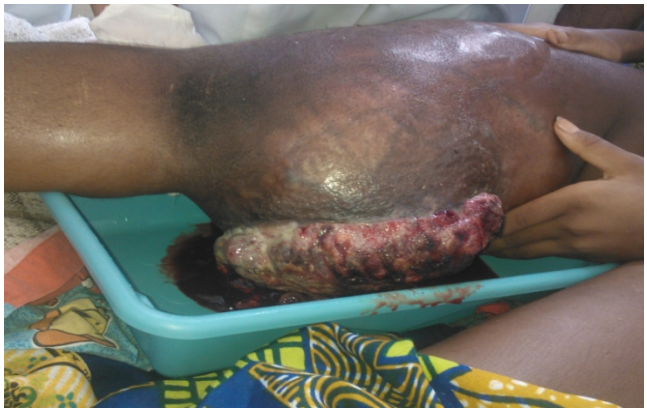

Fig. 2. Fungating osteosarcoma of right thigh

Investigations revealed a haemoglobin level of 3gm/dl. Blood biochemistry and liver function tests were normal but the test for serum alkaline phospatase (from bone) was not available. X-ray of the right limb demonstrated a disintergrating lower third of femur, osteolytic in nature with no evidence of a sequestrum indicating chronic osteomyelitis (Fig. 3). There was surrounding soft tissue swelling around the affected bone.

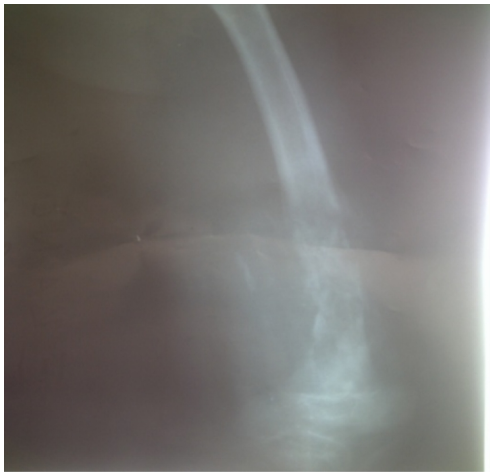

Fig. 3. X-ray of left femur showing osteosarcoma

The differential diagnosis included (1) Osteosarcoma, (2) Ewing's Sarcoma, (3) Chondrosarcoma, (4) malignant giant cell tumour or other variants e.g. malignant fibrous histiocytoma, (5) Fibrosarcoma, (6) Reticulum cell sarcoma and (6) Chronic osteomyelitis. The patient was resuscitated with intravenous fluids following correction of her anaemia with further blood transfusions. She received intravenous analgesia and broad spectrum

antibiotics. A wound swab grew *Pseudomonas aeruginosa*. A chest x-ray and ultrasound scan of the liver excluded metastases. Needle biopsy of the fungating mass confirmed a giant cell-rich osteosarcoma (Fig.4.). Being an apparently locally advanced tumour she was optimized for palliative surgery. The parents gave an informed consent to a high above - knee amputation as the patient refused a disarticulation of the hip which although not as aesthetical and functional may have given a better loco-regional control of the disease.

Apart from a generalized oedema which responded to mild diuretics she made good post operative recovery. Two weeks post amputation she mobilized on a wheel chair with minimal wound pain. A histological examination of the specimen showed a dense plasmacytoid population of small eosinophilic cells with eccentric dark nuclei in close masses between bone lamellae with osteoid consistent with osteosarcoma.

At 2 months follow-up her haemoglobin level was 7gm/dl and she required further blood transfusion prior to commencing chemotherapy.

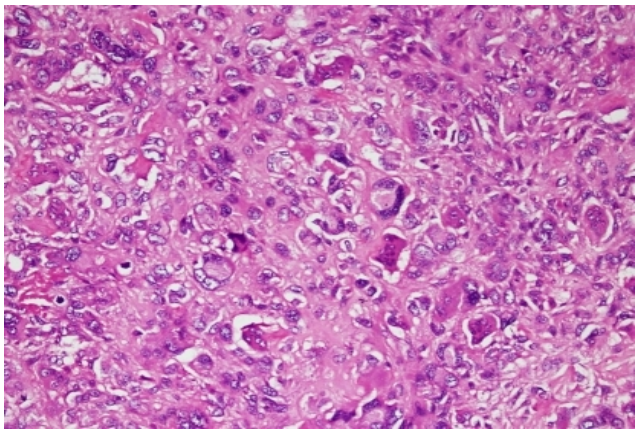

Fig. 4. Photomicrograph showing evenly distributed osteoclast giant cells in an anaplastic stroma; neoplastic osteoid production by stromal cells with nuclear atypia. (H&E x200)

3. SUMMARY

This is a 10 yr-old girl with a past history of a probable unilateral retinoblastoma presenting with a short history (2 months) of a rapidly growing malignant bone tumour of the femur. Clinical examination revealed symptoms and signs of a locally advanced osteosarcoma for which she underwent a palliative high above knee amputation.

4. DISCUSSION

The case highlights the importance of clinically appreciating cancer associations. In this case there was no pathological report of retinoblastoma but it is a logical assumption that she had a retinoblastoma in view of the known association with osteosarcoma. Retinoblastoma is the most common intraocular malignancy in children (~ 3% of all malignancies in children < 15 years of age in USA). 2.5% is hereditary and bilateral, 15% is hereditary and unilateral and 60% is non- hereditary and unilateral. Patients with the hereditary form are at risk of developing secondary neoplasms especially osteosarcomas and soft tissue sarcomas [3].

Meanwhile primary bone tumours are rare, but osteosarcoma is the commonest malignant bone tumour with a peak age of onset in the second decade [4]. The tumours that occur later in life are usually sarcomas arising in Paget's disease or post-irradiation sarcomas[5]. However, some cases of osteosarcoma appear to be familial as in particularly children with familial bilateral retinoblastoma. They have an incidence of osteosarcoma several hundred times that of an age-matched general population. This appears to represent both a genetic predisposition to de novo neoplasia and an increased susceptibility to radiation-induced sarcoma [2,4]. Osteosarcoma and retinoblastoma have a shared chromosomal mechanism revealing a recessive predisposition although inherited as an autosomal dominant trait [1,2]. The retinoblastoma (Rb) gene loci on human chromosome 13 is the first human recessive cancer gene ever cloned and can be used for prenatal diagnosis [2]. Screening of at-risk families and close surveillance of affected individuals for these heritable genetic predisposition syndromes may permit earlier diagnosis and more effective treatment of osteosarcoma in these populations. The long- term follow-up of retinoblastoma survivors is warranted to understand secondary neoplasm risk [3]. A recent retrospective study of 754 patients showed 3% developing 23 secondary neoplasms during a 9 year follow-up after retinoblastoma treatment. The cumulative incidence rates were 2.4% at 10yrs. 4.3% at 20 yrs, 6.4% at 30 yrs, 19.1% at 40 yrs. 65% of the secondary neoplasms were osseous (osteosarcomas) or soft tissue sarcomas (rhabdomyosarcomas, myxofibrosarcoma). The others included Mebonian (eye lid) carcinomas, acoustic neuroma, meningioma, acute myelogenous leukaemia and a neuroendocrine tumour [3]. Ewing's sarcoma has also been observed 2 years following a unilateral retinoblastoma [4].

Osteosarcoma is sometimes discovered when a bone that has been weakened by the cancer breaks after the person has had a minor fall or accident (pathological fracture) as in this case [5,6]. Bone sarcoma often presents as a painful swelling unlike the painless mass of a soft tissue sarcoma. Osteosarcoma occurs near the ends of long bones as in this case unlike Ewing's (round cell) sarcoma which although peculiar to childhood tends to occur in the diaphysis at the middle of long bones [4]. The patient's anaemia was probably due to bone marrow infiltration and the continuing bleeding from the fungating tumour.

A variety of tests and investigations may be needed to diagnose an osteosarcoma. The most important investigation is the plain bone x-ray of the painful part of the bone. It will usually identify a tumour, if present even at a very early stage. The features diagnostic of osteosarcoma seen in the radiograph include metaphyseal location, bone destruction, periosteal elevation and new bone formation. A biopsy of the radiologically suspicious lesion confirms the diagnosis [5]. Other staging tests include blood tests (serum alkaline phosphatase (from bone), lactate dehydrogenase (LDH) whose levels would suggest how advance the cancer is); computerized tomography (CT) with contrast enhancement of the thorax, affected and opposite bone; an isotope bone scan to show if spread to other bones; nuclear magnetic resonance imaging (MRI) to assess extent of primary tumour and a positron emission tomography (PET) scan for distant metastases [7]. These are of increasing value in planning the surgical approach (CT and MRI) and of assessing response to preoperative chemotherapy [5]. Osteosarcoma comprises a family of lesions with considerable diversity in histological features and grades [8]. Knowing the particular type, grade, and stage of the cancer helps the decision on the most appropriate treatment [7]. Most osteosarcomas are high-grade (osteoclast-rich, chondroblastic, telangiectatic, osteoblastic, fibroblastic) but the parosteal and periosteal osteosarcoma type are usually low and intermediate-grade respectively [5],[8]. The giant cell-rich osteosarcoma in this patient is one of the high grade types and is morphologically characterized by a

characteristic scattering of osteoclast –like giant cells. It accounts for only 1-3% of the conventional osteosarcoma cases [5,8,9].

The clinical course of a sarcoma and the patient's prognosis depends ultimately upon the pathology of the tumour. The grade of the tumour which depends on cellularity, anaplasia, mitotic activity and histological evidence of infiltration, is the main histopathological determinant of outcome [8,9]. Osteosarcomas spread by local invasion with bone destruction and extension into neighbouring tissues, through the blood stream predominantly to the lungs and along marrow sinusoids to skip sites in the bone of origin but not through lymphatics to regional nodes unlike soft tissue sarcoma [5]. Thus, the site and grade of the tumour and not the presence of lymph node metastases affects the staging of osteosarcomas. Staging of tumours helps to predict the prognosis. *Stage IA* osteosarcoma is low-grade and is only found within the hard coating of the bone. *Stage IB* is low-grade, extending outside the bone and into the soft tissue spaces that contain nerves and blood vessels. *Stage IIA* is high-grade and is completely contained within the hard coating of the bone. *Stage IIB* is high-grade and has spread outside the bone and into surrounding soft tissue spaces that contain nerves and blood vessels. *Stage III* osteosarcoma can be low or high-grade and is either found within the bone or extends outside the bone and has spread to other parts of the body, or to other bones not directly connected to the bone where the tumour started. Most osteosarcomas are stage IIB [5,6,8,9]. However, although most osteosarcomas are thought to be localized when first found, despite imaging tests most patients are likely to have micrometastases [7].

Treatment for high-grade osteosarcoma will therefore depend on a number of factors including the size, position and stage of the tumour [6,7]. Combination chemotherapy is given before (neoadjuvant) and after (adjuvant) surgery, which takes the form of limb-sparing en bloc tumour removal with endoprosthetic bone reconstruction or bone grafting - except when there is gross soft –tissue invasion when amputation is required as in this case. Most non- metastatic osteosarcomas (Stages IIA-IIB) are treated with 2-3 cycles of neoadjuvant chemotherapy for about 10 weeks and 3-4 cycles of postoperative (adjuvant) chemotherapy for up to a year [7]. Neoadjuvant chemotherapy is usually given to downsize the main tumour before surgery but not for this extremely large and ulcerating tumour. Patients whose tumours responded poorly may get a different chemotherapy regimen after surgery. Adjuvant chemotherapy would help reduce local recurrence of the tumour and improve cure rate by attacking the putative micrometastases. Radiotherapy in combination with restricted surgery is utilized for tumours in sites where the scope for excisional and reconstructive surgery is limited such as in the head, neck and trunk and where there is macroscopic or gross residual disease [7]. Radiotherapy can occasionally provide long-term, local symptom control for localized unresectable osteosarcomas [5,9].

The overall 5-yr survival following current treatment regimes for osteosarcoma is between 40-50%. Other factors linked with a better survival include: being younger, being female, tumour being on arm or leg (as opposed to hip bones), tumour being completely resectable, a normal blood alkaline phosphatase and LDH levels and a good response to chemotherapy [10].

The prognosis of osteosarcoma have increased steadily over the past 25 years because of the multidisciplinary approach in management involving the radiologist, oncologist, pathologist and surgeon [10,11].

5. CONCLUSIONS

This case illustrates the importance of relating clinical observations with disease associations. In this case there is an association between a retinoblastoma and the later occurrence of osteosarcoma. A child with a retinoblastoma should be followed up very closely during childhood and adolescence for possible tumour recurrence or the development of an associated malignancy such as osteosarcoma.

CONSENT

All authors declare that 'written informed consent was obtained from the patient (or other approved parties) for publication of this case report and accompanying images.

ETHICAL APPROVAL

Not applicable.

CONFLICT OF INTEREST

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. Authors have declared that no competing interests exist.

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