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Review Article

Skeletal involvement in Burkitt's lymphoma: a comprehensive review

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ABSTRACT

Burkitt's lymphoma, a highly aggressive form of non-Hodgkin lymphoma, exhibits a distinctive predilection for rapid growth and systemic dissemination. While its primary manifestation is often observed in the lymphatic system, orthopaedic involvement has been increasingly recognized. This review synthesizes current literature to comprehensively explore the orthopaedic implications of Burkitt's lymphoma, encompassing clinical presentation, diagnostic challenges, treatment modalities, and associated outcomes.

Keywords: BL, Orthopaedic manifestations, Skeletal involvement, Diagnosis, Treatment, Musculoskeletal system

INTRODUCTION

Burkitt's lymphoma (BL) is a malignant proliferation of undifferentiated B lymphocytes that most often affects children.[1] In endemic areas of Africa, the jaws are the sites most frequently involved. In non-endemic areas of North America, the jaws are involved in only 15-18% of cases.[2]

BL is a malignancy known for its aggressive nature, typically affecting the lymphatic system.[1] However, its impact on the musculoskeletal system, though less common, poses significant clinical challenges.[3] The gastrointestinal system, gonads, mesentery, peritoneum, retroperitoneum, head, and neck region are among the possible sites of involvement in a paediatric case of BL.[4]

Large soft-tissue masses eventually result from the subperiosteal new bone development that the bony lesion in BL eventually causes. Lesion begins as small osteolytic foci in the medulla coalesce and penetrate the cortex.[3]

The purpose of this review paper is to investigate and analyse the orthopaedic consequences of BL, including clinical manifestation, difficulties in diagnosis, available treatment options, and related consequences.

PATHOPHYSIOLOGY

BL's orthopaedic symptoms are caused by malignant B-cells directly invading bones and joints, which adds to pathophysiology of this unusual relationship.[3] BL frequently spreads hematogenously, affecting many organs and tissues, including bones.[5] Bone marrow is invaded by malignant B-cells, which destroy bone and interfere with normal hematopoiesis. Predilection for jaw and face bones is 1 characteristic of bony involvement in BL.[6] Few case reports involving shorter cases, however, have been published and have been linked to spine, pelvis and long bones. Review of articles available for involvement of bone in BL (Table 1).[7-12] Rate of proliferation of BL's cancerous cells is remarkably great.[13] This quick development raises possibility of pathological fractures and compromises bone structure by forming osteolytic lesions.[3] Immune dysregulation, especially weakened cell-mediated immunity, is frequently linked to BL. This dysregulation adds to invasiveness of malignant B-cells, which breaks down affected bones' structural integrity and causes widespread bone loss.[14] An important factor in development of disease is interaction between BL cells and bone microenvironment. Usual equilibrium between bone creation and resorption is upset by malignant cells, which encourage bone breakdown.[5]

Table 1: Review of literature regarding skeletal involvement of BL.

Author/ year	Sample size	Patient details	Site involved	Presentation	Diagnosis	Management	Remarks
Picon et al, 2010[11]	1	3-year-old boy	Proximal tibia	Feverish cold limping of right lower limb	USG: subperiosteal collection bone scan: uptake increase, MRI: changes in marrow Bone biopsy: inconclusive FNAC from cervical lymph node: BL marrow IHC: Conclusive	Chemotherapy	
Seo et al, 2014[10]	1	40-year-old Asian man	Thoracic spine: T2 to T4	Progressive pain and weakness in his lower extremities	MRI: Elongated intraspinal extramedullary mass from T2 to T4 liver biopsy: B-cell type lymphoma IHC: CD20-positive	Chemotherapy combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). Radiation treatment of 200cGy per fraction (3000cGy in 15 fractions)	Died by massive pulmonary thromboembolism at 13 weeks post-operatively
Cha et al, 2014[7]	1	3-year-old girl	Distal femur	Pain in hip and knee joints	USG: Joint fluid MRI: Periosteal reaction		
Cadavid et al, 2017[8]	1	8-year-old boy	Left ilium	Fever mass in left inguinal region	X-ray: eccentric lytic lesion, MRI: multiple lymph-adenopathies, USG: Hepatospleenomegaly, retroperitoneal lymphadenopathy Biopsy:malignant lymphoid infiltrate, IHC: Positive CD20, bcl-6, and CD10 markers	Chemotherapy (cytarabine, etoposide, ifosfamide)	Nodal and intracardiac metastases
Mechtou-ne et al, 2021[12]	1	49-year-old female patient	Upper end tibia	Pain of the left knee and abdominal pain	X-ray: fracture of the upper end tibia CT scan: Osteolytic epiphyseal-metaphyseal tissue damage of the tibia with soft tissue invasion. Biopsy: malignant lymphoid infiltrate with large size cells, multiple nucleoli, a very high proliferative rate, and frequent mitotic figures. IHC: CD20+, BCL 6+, and CD10 +, MUM1+,	Chemotherapy: R-CODOX-M (rituximab 375 mg/m^2, doxorubicin 40 mg/m^2, cyclo-phosphamide 800 mg/m^2, cytarabine 70 mg intrathecal, methotrexate 300 mg/m^2 IV/R-IVAC (rituximab 375 mg/m^2 IV, etoposide 60 mg/m^2 IV, ifosfamide 1.5 g/m^2, mesna 300 g/m^2 IV, cytarabine 2 g/m^2 IV, methotrexate 12 mg intrathecal).	
Regmi et al, 2022[9]	1	11-year-old female	Pelvis	Pain and swelling over the left hip region	X-ray: destructive lytic lesion arising from left hemipelvis, MRI: heterogeneously enhancing and erosive mass lesion in left hemipelvis, Bone scan: primarily vascular, osseous neoplasm, IHC: CD 20/CD79a/CD19 positive	Chemotherapy: Cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate (CODOX-M)/ifosfamide, etoposide, and high-dose cytarabine (IVAC)	

ORTHOPAEDIC MANIFESTATIONS

Although lymph nodes are frequently the site of its major manifestation, BL can also exhibit unique orthopaedic signs and symptoms that point to a possible musculoskeletal involvement. Bone pain, either localised or diffuse, is common in patients with BL and is frequently accompanied by soreness. This symptom is caused by malignant B-cells that invade the bone marrow and cause lytic lesions, growing rapidly.[3]

Pathological fractures are more likely due to the aggressive nature of BL, which is marked by fast cell proliferation and osteolytic bone lesions.[15] Because of the weakened bone structure, even minor stress can lead to fractures.[12] The infiltration of lymphoma cells into the soft tissues around the joints may cause swelling in the limbs, especially in the extremities.[3] Pain, stiffness, and functional impairment can result from joint involvement. When joints are impacted, there could be a noticeable decrease in range of motion. This limitation is frequently brought on by the invasion of a tumour into the soft tissues or joint spaces, which results in mechanical constraints.[12]

Rarely, people with BL that affects the spine which may have neurological symptoms such weakness, back discomfort, or neurological deficits. Complications from spinal cord compression can be rather serious.[10] Systemic signs, which are not unique to orthopaedic involvement, can accompany musculoskeletal manifestations and indicate the overall aggressive nature of BL.[3]

DIAGNOSTIC CHALLENGES

BL is a relatively uncommon cancer, especially in various areas of the world.[2] Because of this rarity, medical professionals might not be as familiar with it, which could lead to mistakes or incorrect diagnoses.[16] Given that BL is notorious for growing swiftly, orthopaedic issues could develop rapidly as well. Osteolytic lesions can develop quickly, and the accompanying symptoms can provide an abrupt and severe presentation.[3,15] This can make it difficult for clinicians to differentiate BL from other bone disorders.

While identifying orthopaedic issues requires the use of imaging studies like MRIs, CT scans, and X-rays, interpreting these pictures can be difficult.[5] Radiologically, BL might show up as soft tissue involvement, periosteal responses, and osteolytic lesions, among other things.[9] It might be difficult to distinguish BL from other bone tumours or infectious diseases based alone on imaging results due to the variety in radiological patterns. The key to diagnosing BL is obtaining a tissue biopsy for histological analysis.[17] However, there might be variation in the histopathological findings, making it difficult to differentiate BL from other high-grade B-cell lymphomas or non-neoplastic diseases. Accurate diagnosis requires molecular specialised knowledge including immunohistochemistry and molecular analysis.[18]

Diagnosing BL-related orthopaedic issues often needs a multidisciplinary approach comprising orthopaedic surgeons, oncologists, radiologists, and pathologists. While coordinating efforts across many specialties can be logistically tough, it is necessary to ensure a thorough evaluation and accurate diagnosis.[17,19]

TREATMENT STRATEGIES

Chemotherapy is a crucial component of BL treatment, making a substantial contribution to the control of this extremely aggressive B-cell lymphoma.[20] Chemotherapy for BL patients has a complex effect on orthopaedic outcomes that takes into account both systemic disease and musculoskeletal symptoms. The mainstay of BL management is chemotherapy because of the disease's fast development and systemic dissemination. High response rates to aggressive regimens like CODOX-M/IVAC or intensive combination chemotherapy regimens like cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) have been shown in BL patients.[21] The goals of these regimens are to control the spread of the disease burden and achieve quick remission. Combining chemotherapy with targeted drugs to treat BL is being investigated as a result of advancements in cancer therapies.[22] Combined with chemotherapy, targeted medicines like rituximab (an anti-CD20 monoclonal antibody) have been demonstrated to produce better results. Potentially improving the overall response to treatment, these methods may have particular effects on orthopaedic outcomes.[23]

Orthopaedic issues including pathological fractures or spinal cord compression may occasionally necessitate surgery.[10,12] Chemotherapy induces cancer shrinkage and decreases the amount of skeletal involvement, which can lead to more successful surgical treatments and improved postoperative recovery.[20] Because BL destroys bone so quickly, pathological fractures are a common result of the condition. The goals of the surgical procedure are to lessen discomfort, encourage early mobilisation, stabilise and fixate the damaged bones, and stop additional fractures.[12] Decompressive surgery may be required in cases of spinal cord compression brought on by BL involvement. This entails lowering or eliminating the mass effect on the spinal cord, usually by resecting a tumour or performing a laminectomy. In order to avoid long-term neurological impairments, prompt intervention is essential.[10]

The importance of radiation in resolving musculoskeletal indications of BL is considerable, and it is commonly adopted as part of a multimodal treatment approach.[24] Ionising radiation is used in radiotherapy, a localised treatment, to target and kill cancer cells. More accurate targeting of cancer areas is possible with advanced radiation techniques like intensity-modulated radiation treatment (IMRT) or stereotactic body radiation therapy (SBRT), which also minimise damage to nearby healthy tissues. This is especially crucial in musculoskeletal

regions where there may be close closeness of essential tissues.[25,26]

PROGNOSIS AND OUTCOMES

A number of variables, such as the severity of the disease, the type of treatment used, the age of the patient, and general health, might affect the survival rates and results associated with BL, with a particular emphasis on musculoskeletal consequences.[3] BL is renowned for responding quickly to intensive treatment modalities, such as combination chemotherapy regimens. In BL, musculoskeletal issues may affect the final result.[21] Pathological fractures, joint damage, and other orthopaedic difficulties could result from the tumor's rapid growth and potential involvement of the skeleton.[12] With estimates ranging from 70% to 90% or greater in certain circumstances, the overall survival rates for BL can be fairly good.[27]

Long-term orthopaedic consequences and difficulties may arise from the therapy of BL, especially when musculoskeletal disorders are present.[17] These could result from the aggressiveness of the disease, the potency of the available treatment options, and the way the musculoskeletal system is affected. Osteonecrosis, which affects the blood supply to bones and causes bone destruction, can occur as a side effect of intensive chemotherapy, especially when combined with drugs like high-dose methotrexate. Long-term problems with joint function, mobility, and bone integrity may arise from this.[21] Treatment effects on growth and development in paediatric patients are a concern. Radiation and chemotherapy may have an impact on long bone growth plates, which could result in aberrant growth.[21]

Long-term functional damage may result from surgical procedures, particularly joint resections or reconstructions. Overall mobility and quality of life may be impacted by joint stiffness and a restricted range of motion.[7,11,12] Radiation therapy can cause fibrosis in the joints and soft tissues, which can make them less flexible and rigid. This could affect one's ability to function independently and in daily life.[24] Long-term orthopaedic issues may impact one's overall well-being, self-esteem, and body image psychologically. Evaluations of quality of life should take into account the psychological effects on survivors in addition to physical results.[28]

CONCLUSION

Rapid development and aggressive conduct are hallmarks of BL, which can deeply affect the musculoskeletal system and cause orthopaedic issues that call for a comprehensive therapy. The likelihood of spinal cord compression, infiltration of bone marrow, and the disease's preference for the jaw and face bones highlight the significance of an early diagnosis and thorough examination. Oncologists, orthopaedic surgeons, radiologists, and rehabilitation specialists must work together during treatment, which consists mostly of intense chemotherapy. The complex terrain of bone loss emphasises the need for continued interdisciplinary collaboration in order to optimise patient treatment, resolve complications, and improve survivorship results. Long-term effects include growth anomalies, joint stiffness, and osteonecrosis risks.

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