A unique presentation of destructive shoulder arthropathy in the chronic phase of chronic myeloid leukaemia

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Abstract

We present a previously unreported case of rapidly progressing, destructive shoulder arthropathy as an initial presentation of chronic phase chronic myeloid leukaemia. This patient initially presented to clinic for consideration of an arthroplasty for symptom relief; however, her loss to follow-up yielded a rapid progression of her symptoms. Bone marrow aspirate and targeted biopsy of the humeral head excluded blast cell crisis, in contrast to previously reported cases. She was treated conservatively with medical management of her underlying disease. Although leukaemic arthritis is a recognized phenomenon, chronic myeloid leukaemia is not known to cause bone destruction of this kind, particularly in the absence of blast crisis. Medical treatment with a tyrosine kinase inhibitor provided a dramatic improvement in our patient's pain, without the risk of attempted arthroplasty in unknown bone quality. We describe a unique presentation of severe bone destruction as a manifestation of chronic myeloid leukaemia in the absence of blast crisis. This should be considered as a rare differential diagnosis in joint arthropathy and may be appropriately managed initially with medical therapy, whereas future arthroplasty comprises uncharted territory in unknown bone quality.

Keywords

blast cell crisis, chronic myeloid leukaemia, chronic phase, leukaemic arthritis, shoulder arthropathy, tyrosine kinase inhibitor

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Introduction

We present a previously unreported case of rapidly progressing, destructive shoulder arthropathy as an initial presentation of chronic phase chronic myeloid leukaemia. Although leukaemic arthritis is a recognized phenomenon, chronic myeloid leukaemia is not known to cause bone destruction of this kind, particularly in the absence of blast crisis. Medical treatment with a tyrosine kinase inhibitor provided a dramatic improvement in our patient's pain, without the risk of attempted arthroplasty in unknown bone quality.

Case report

We present the case of an independent 67-year-old, right-hand dominant, South African lady who was referred to our clinic for a second opinion, having been refused an arthroplasty following a longstanding history of

right shoulder pain. She had a background of hypertension and chronic anaemia.

This patient initially presented to a local hospital in July 2014 with a 2-year history of bilateral shoulder pain, most severely affecting the right side. This was poorly controlled by analgesia and steroid injections, significantly hindering her activities of daily living. There was no history of septic arthritis. Clinical examination identified a right shoulder drop with universally reduced range of movement and significant wasting of her supraspinatus, infraspinatus and deltoid muscles. Radiographs (Figure 1) and a magnetic resonance imaging (MRI) scan (Figure 2) were arranged for her at

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Figure 1. Anteroposterior radiograph of right shoulder 2014.

Figure 3. Anteroposterior radiograph right shoulder 2015.

Figure 2. T1W Magnetic resonance imaging scan of right shoulder 2014.

Figure 4. T1W Magnetic resonance imaging scan of right shoulder 2015.

this time alongside haematology and gastroenterology clinic referrals on account of her thrombocytosis and iron deficient anaemia, respectively. MRI of the right shoulder illustrated severe degenerative change of the glenohumeral joint with erosion of the articular surfaces alongside a 25% loss of volume of the humeral head. A supraspinatus tendon rupture was also noted. The surgeon at this time felt the erosion of the glenoid and humeral head was too severe for placement of a glenoid component and elected to manage her conservatively with analgesia including naproxen and co-codamol. She was then referred to our clinic for a second opinion.

This patient first attended our hospital in January 2015 for reassessment, her images were reviewed and she was tested for sickle cell disease, which was negative. She was subsequently listed for a shoulder arthroplasty; however, she declined surgery at this time to allow her to visit her family abroad, and was lost to follow-up.

In October 2015, this patient was re-referred to our hospital with a view to be re-listed for an arthroplasty.

She had experienced a gradual progression of her symptoms, developing associated fatigue and weight loss over the last year. On examination, her range of movement was limited to 10° to 15° in each direction and her neurology was normal. Radiographs demonstrated progressive rapid destruction of both shoulders, with the right side being worst affected (Figure 3). She was then investigated with repeat MRI scans and blood tests. The results demonstrated on-going normocytic anaemic, thrombocytosis and a neutrophilia. Serum testing for infective causes was negative. Her MRI (Figure 4) highlighted severe glenohumeral joint destruction with high marrow signal indicative of leukaemic infiltration. The humeral head had almost entirely disappeared, and her infraspinatus tendon was ruptured alongside her supraspinatus tendon. Similar findings, although less marked, were observed on the left shoulder (Figure 5). There was marked osteoarthritis in both acromioclavicular joints, which had progressed over time; however, there was no evidence of leukaemic

Figure 5. Magnetic resonance imaging scan of left shoulder 2015.

infiltration. This patient's rotator cuff arthropathy was present on her initial MRI and there was no evidence of soft tissue myeloid invasion, suggesting that this was longstanding. By contrast, she developed rapid bone destruction of her humeral head between MRI scans, with no evidence of osteonecrosis or infection, suggesting this was solely a result of invasion by leukaemia.

An urgent haematology referral was made and the patient was diagnosed with chronic myeloid leukaemia (CML) in November 2015, following a bone marrow aspirate, trephine biopsy and cytogenetic and molecular testing. These tests were consistent with chronic phase CML, although this is not previously known to be associated with bony destruction of this kind and so a diagnostic open shoulder biopsy was arranged for December 2015, aiming to look for local transformation or coexistent pathology. The biopsy revealed a macroscopically liquefied marrow. Histologically, there was a weakened bone texture and markedly hypercellular marrow for her age group; the marrow contained almost entirely haemopoietic cells rather than an even split between such cells and fat spaces as is normally observed. Additionally, there was a dramatically increased myeloid to erythroid cell ratio but no evidence of transformation into an acute leukaemia because her blast count remained low. There was no evidence of other pathology. Her bilateral shoulder degeneration was therefore attributed to chronic phase CML, for which she was started on imatinib 400 mg OD in January 2016, with the aim of controlling her CML to prevent further bone destruction.

This patient has shown steady improvement since initiating her medical treatment. Her haemoglobin remains stable and her platelet and neutrophil counts began to fall after 2 weeks of treatment. Subsequently, she was followed up closely over a 2-month period

Table 1. Full blood count results pre- and post-tyrosine kinase inhibitor therapy.

Full blood count	Pre-treatment (October 2015)	6 months after treatment (June 2016)
Red blood cell count ($\times 10^{12}/L$)	3.76	2.86
White blood cell count ($\times 10^9/L$)	18.1	3.7
Haemoglobin (g/L)	99	93
Haematocrit	0.30	0.27
Mean cell volume (fL)	80.3	94.4
Platelets ($\times 10^9/L$)	691	473
Neutrophils ($\times 10^9/L$)	14.0	1.3
Lymphocytes ($\times 10^9/L$)	3.5	1.7
Monocytes ($\times 10^9/L$)	0.6	0.6
Eosinophils ($\times 10^9/L$)	0.0	0.0
Basophils ($\times 10^9/L$)	0.1	0.1

where her blood tests have continued to improve (Table 1) and her shoulder pain reduced. Molecular analysis in June 2016 confirmed that she is in a major molecular remission. Recent clinical examination demonstrated 80° forward flexion, 60° abduction, 10° external rotation and internal rotation to buttocks around her right shoulder. She has maintained her independence in her activities of daily living, despite ongoing discomfort, and mobilises with a rollator.

Discussion

Leukaemia is a malignant neoplasm of the bone marrow resulting in an abnormal proliferation of immature blood cells. This gives rise to inadequate and irregular haematopoiesis, which manifests itself depending on the cells affected. Classification is based upon on these affected cells (myeloid or lymphoid) alongside the course of the disease (acute or chronic) and is essential for understanding the presentation, management and ultimate prognosis of patients. This classification is being refined continually as we come to understand more about the genetic changes involved in leukaemogenesis.

CML is classed as one of the myeloproliferative neoplasms and it mainly manifests as bone marrow myeloid hyperplasia and neutrophil leukocytosis, although thrombocytosis is also seen. Untreated, CML is bi- or

triphasic, consisting of a chronic phase, accelerated phase and subsequent blast crisis. Throughout the chronic phase, leukaemic cells are minimally invasive and remain largely confined to haematopoietic tissue, whereas tissue invasion and damage occurs with blast crisis. Blast crisis resembles an acute leukaemia with a poorer prognosis,¹ although modern therapy can overcome this to some extent.² CML is the paradigm for molecular based therapy of neoplasia. It has been found to be consistently associated with the presence of the BCR-ABL1 fusion gene on the Philadelphia chromosome and specific tyrosine kinase inhibitors (TKI) have been engineered which have had a profound impact on CML treatment, such that many patients can expect to have a normal lifespan.^{3,4}

Leukaemia traditionally presents with fever, fatigue, weight loss and the consequences of deranged blood counts; however, leukaemic cells can infiltrate normal organs, producing a range of possible symptoms. Leukaemic arthritis (LA) is a recognized feature of these malignancies but usually without marked bone destruction; it is most commonly acknowledged in children with acute forms of the disease; however, it may also affect adults as well.^{5,6}

Leukaemia can cause musculoskeletal pain because of other causes: bone pain without destruction is common in childhood acute lymphoblastic leukaemia but not typically seen in adult disease; infiltration of muscle has been reported and mass lesions can occur

called chloromas; neuropathy is not typically seen, although central nervous system infiltration is well recognized, particularly in lymphoid leukaemias, but pain is uncommon.⁷ Soft tissue infiltration, unlike bone, will completely resolve given effective treatment with minimal residual damage.

The aetiology of LA has been widely deliberated and synovitis as a result of leukaemic infiltrates within the synovial membrane is a well-documented cause.⁸ LA presents as hot, swollen and tender joints that are often symmetrical. It generally affects large joints such as shoulder or knee; however, diagnostic biopsy can be problematic because of the focal nature of leukaemic infiltrates.⁸⁻¹⁰ LA can occur at any time during the course of leukaemia; there are numerous reports of LA presenting as an initial presentation of disease in children,⁶ and less commonly adults.^{9,11} Although osteopaenia and osteolytic lesions have been identified in LA patients,⁵ bone destruction to the degree as illustrated in our case has not been previously reported, especially in the absence of a blast crisis.

There are only few reports of LA presenting as an initial disease presentation in CML, and they describe blast crisis.¹² Characterization of the accelerated phase has historically been vague; however, definitions have subsequently been proposed by the World Health Organization (WHO) and European LeukaemiaNet (ELN) based upon peripheral blood tests, marrow blast count and response to therapy (Table 2).^{13,14}

Table 2. Definitions of chronic myeloid leukaemia (CML) accelerated phase CML (as proposed by the World Health Organization and European LeukaemiaNet), alongside our patients matching of criteria.

WHO criteria ¹³	European LeukaemiaNet expert panel criteria ¹³	Patient in present study
Blast cells in blood or bone marrow 10% to 19%	Blast cells in blood or bone marrow 15% to 29%; blast cells + promyelocytes in blood or bone marrow >30% with blast cells <30%	Blast cells <10%
Serum basophils $\geq 20\%$	Serum basophils $\geq 20\%$	Serum basophils <20%
Thrombocytopenia unresponsive to therapy (platelets $< 100 \times 10^9/L$)	Persistent thrombocytopenia (platelets $< 100 \times 10^9/L$) unrelated to therapy	Platelets = 473 (post-therapy)
Thrombocytosis unresponsive to therapy (platelets $> 1000 \times 10^9/L$)	Not included	Platelets = 473 (post-therapy)
Splenomegaly and increasing WBC count unresponsive to therapy	Not included	WBC responsive to therapy, normal size spleen
Cytogenetic evidence of clonal evolution (the appearance of additional genetic abnormalities)	Not included	Not evident

WBC, white blood cell.

Our case demonstrates an adult patient presenting with marked symmetrical joint destruction of the shoulder as an initial presentation of CML in the chronic disease stage, confirmed by marrow and targeted bone biopsy indicating a below threshold blast cell count. Ultimately, medical treatment of the underlying diagnosis with TKIs provided a marked improvement in her symptoms, allowing her an increased range of movement around both shoulders alongside a significant improvement in her arthralgia and peripheral blood tests. Although she does not meet the above WHO and ELN criteria, it could be argued that marked bone destruction to this degree should independently contribute to a diagnosis of accelerated phase CML because this could impact upon management in younger patients.

Without the definitive diagnosis, no accurate prediction of bone quality could be made and so insertion of an implant would have carried significant risk. In our case, the patient was delayed to follow-up for 6 months, during which time there was significant development of her bone destruction. This contributed to her clinical picture, facilitating a diagnosis and avoiding arthroplasty surgery. During her biopsy, it was noted that she had very weak bone architecture, which would likely lead to implant failure. After discussion with a haematologist, it was considered that the chance for recovery of bone quality was uncertain, despite TKI therapy, because this case is a rarity.

In summary, LA is a well-recognized complication of leukaemia, particularly in children with acute forms of the disease but, ultimately, it can present at any time. The severity of bone destruction illustrated in this adult patient in chronic phase CML has not previously been reported but could implicate the diagnosis of the accelerated phase. This case demonstrates a potential rapid progression of this condition and highlights the importance of considering it as a rare differential to allow early diagnosis and initiation of medical therapy.

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Ethical review and patient consent

The patient has provided written informed consent for this case report and associated images to be used.

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