



A Case of Rhabdomyolysis and Polyarticular Inflammatory Arthritis May be the Initial Presentation of Chronic Myelogenous Leukemia (CML)

Yelliann Ruiz-Irizarry^{1*} and Petros Efthimiou²

¹Internal Medicine PGY-3, New York Methodist Hospital, USA

²Rheumatology Division, New York Methodist Hospital, Weill Cornell Medical College Affiliate, USA

*Corresponding author: Yelliann Ruiz-Irizarry, Internal Medicine PGY-3, New York Methodist Hospital, Weill Cornell College of Medicine Affiliate, USA, E-mail: yelliannruiz@hotmail.com

Abstract

Rhabdomyolysis and inflammatory arthritis are common rheumatologic conditions that manifest in people of all ages. Proximal muscle weakness associated to rhabdomyolysis is frequently the initial presentation of inflammatory myopathies such as dermatomyositis (DM) and polymyositis (PM) both, extensively described in literature to be related to paraneoplastic process. Inflammatory arthritis has been associated to certain paraneoplastic syndromes, but not in relation to Chronic Myelogenous Leukemia (CML). CML accounts for 15 to 20 percent of leukemias in adults with a slight male predominance and a median age at presentation of 50 years. We report a case of a 28 year-old male with no significant medical history who presented with initial complaints of severe bilateral thigh pain for 4 days after mild exercise associated with inflammatory polyarthritis, leukocytosis, rhabdomyolysis, and renal injury as a De Novo diagnosis of CML. Our treatment regimen for the associated inflammatory polyarthritis and rhabdomyolysis included corticosteroids with achieved complete resolution of symptoms after 6 weeks. It is reasonable to consider that acute rhabdomyolysis could be a rare initial presentation of CML. This association should prompt reconsideration of the avoidance Imatinib for CML. A first line agent treatment for CML is the tyrosine kinase inhibitor Imatinib, which has been reported to cause rhabdomyolysis in several patients.

Case Presentation

A 28 year old male with no significant past medical history presents to the emergency department with severe bilateral thigh pain for 4 days after engaging on mild aerobic activity. His thigh pain was restricting his ambulation and daily life activities, was better at rest, worse with any movement especially getting up from sitting to standing position and when climbing stairs, and did not improved with 2 tablets of ibuprofen. He noted a dark brown discoloration of the urine and bilateral swelling of the hands and knees 1 day prior admission. He admitted 4 alcoholic drinks 2 days prior admission. He had flu-like symptoms 2 weeks prior admission that resolved spontaneously. His last physical exam was three years prior with normal blood work. He had no prior surgical history. His family

history was positive for a grandmother with lung cancer, and Crohn's disease in mother and brother. He was previously tested negative for Crohn's disease by endoscopy studies. He was a weekly drinker of 4-5 beers. He denied drug use. He was sexually active without any sexually transmitted disease in the past. He has had a clerical job at the city transit department.

On examination, the patient's blood pressure was 160/100, his heart rate was 105; other vitals and oxygen saturation were normal. He had bilateral hand swelling and synovitis, and mild bilateral knee swelling with synovitis. He also had bilateral thigh myositis with decrease proximal muscle strength, limited range of motion secondary to pain, and mild pitting edema up to mid-shins. The remainder of the examination was normal. His laboratory reports revealed a white blood cell count was 78 K/ μ L, RBC 4.5 M/uL, hemoglobin 12.2 g/dL, hematocrit 37.9%, red cell width 18.3%, and platelets were 477 K/mL. Blood urea nitrogen and creatinine were elevated at 21 mg/dl and 1.4 mg/dl, respectively. Aspartate aminotransferase (AST) was elevated at 3,206 u/L and alanine aminotransferase (ALT) was normal at 598 u/L. Serum uric acid was 9.0 mg/dL and lactate dehydrogenase was 2152 u/L. Creatine kinase and myoglobin were elevated at 221,400 u/L and 15,300 mcg/L, respectively. Aldolase was elevated to more than 500 u/L. C Reactive protein was elevated at 21.7 mg/L. Serum albumin, total protein, total bilirubin, alkaline phosphatase, gammaglutamyl transferase (GGT), prothrombin time, and partial thromboplastin time were normal. Common viral and bacterial disease along with complete autoimmune workup was all negative. Leukocyte alkaline phosphatase was normal. The urinalysis showed 100 mg/dL protein on dipstick, a large qualitative study for blood, and on microscopy there were 2 RBC/HPF, 3 WBC/HPF, and rare graded amorphous crystals/HPF. A urine toxicology test was negative.

On day one of admission, he was started on aggressive IV fluid hydration with normal saline and a sodium bicarbonate drip. On day 2 of admission, he complained of persistent thigh weakness and pain and knee pain that were partially improved with hydromorphone. He noted that his urine became lighter. His vital signs normalized. His liver enzymes, creatine kinase, and LDH were trending down. His acute kidney injury was resolved. His x rays of the hands, wrists, and

knees did not show an erosive pattern. CT of the chest, abdomen, and pelvis was unremarkable except for extensive splenomegaly. He was continued on IV hydration with normal saline. He was started on Methylprednisolone 20 mg IV every 8 hours. On day 3 of admission, his symptoms were improved and finally he could get out of bed by himself. Peripheral flow cytometry revealed increased neutrophilic cells with all stages of maturation, including 1.1% atypical blasts. On day 4 of admission, his lower extremity edema and synovitis resolved. He was able to ambulate without assistance. Fluorescence in situ hybridization (FISH) was positive for BCR/Abl translocation. On day 5 of admission, he had a bone marrow biopsy. Methylprednisolone was discontinued and he was started on oral prednisone that was tapered in 1 month. His bone marrow biopsy was morphologically consistent with a myeloproliferative neoplasm. CML confirmed by FISH and Reverse Transcriptase Polymerase Chain Reaction. Aberrant immunophenotypes were detected by flow cytometry (increased CD56 positive neutrophils, ~1% CD7 positive blasts). He was started on Nilotinib 200 mg oral twice a day.

Discussion

CML is a myeloproliferative neoplasm characterized by the uncontrolled production and proliferation of mature and immature granulocytes with fairly normal differentiation. CML typically results from the abnormal fusion protein of the BCR-Abl gene that regulates the tyrosine kinase activity. CML clinical course is described as triphasic or biphasic as it progresses from a chronic phase to an accelerated phase and on to a terminal blast crisis. Exposure to ionizing radiation is the only known risk factor [1]. The clinical findings at diagnosis of CML vary among patients. More than half of patients are asymptomatic, but others might present with systemic symptoms such as fatigue, malaise, weight loss, sweating, abdominal fullness, and bleeding episodes [2]. Acute gouty arthritis may also present at this time, due to overproduction of uric acid. The diagnosis is commonly suggested by characteristic findings on the peripheral smear. Genetic testing for the Philadelphia chromosome the BCR-Abl fusion gene or the fusion mRNA gene product by conventional cytogenetic analysis (karyotyping), fluorescence in situ hybridization (FISH) analysis, or by reverse transcription polymerase chain reaction (RT-PCR) confirms the diagnosis.

The inflammatory myopathies dermatomyositis (DM) or polymyositis (PM) share the common feature of immune-mediated muscle injury. Clinical and histopathological distinctions between these conditions suggest that different pathogenic processes underlie each of the inflammatory myopathies. One study reported in the literature, estimated that the incidence of cancer for patients with DM was increased five- to sevenfold compare with the general population [3]. The precise links between malignancy and inflammatory myopathy remain incompletely understood [4]. Regenerating cells in myositis muscle but not in normal muscle express high levels of myositis-specific autoantigens suggesting that the link between malignancy and inflammatory myopathy relates to the expression of common autoantigens between cancer tissue and muscle tissue in some patients with DM and PM. The peak incidence of malignancy diagnosis occurs within the two years of the inflammatory myopathy diagnosis, but mostly commonly the malignancy is diagnosed within a period of 7-14 days of the inflammatory myopathy presentation [5,6]. Malignancies can be diagnosed before, simultaneously with, or after the diagnosis of inflammatory myopathy. Adenocarcinomas of the cervix, lung, ovaries, pancreas, bladder, and stomach account for approximately 70 percent of the cancers associated with inflammatory myopathies [6,7]. In many cases, the inflammatory myopathy responds to successful therapy of the underlying malignancy. Cancer-associated myositis in adults has been associated in several studies with antibodies but more study is required to determine the utility of these autoantibodies for cancer screening in patients with myositis.

Rhabdomyolysis related to tumor lysis syndrome is a well-known entity that is highly associated to acute leukemias. Chemotherapy induced-rhabdomyolysis have been also described in literature to minimal extent, on the tyrosine kinase inhibitors (TKI) use, specifically

Imatinib on the treatment of CML. Imatinib is used in the treatment of multiple cancers, most frequently Philadelphia chromosome-positive (Ph+) CML. In Ph+ CML cells, one tyrosine kinase enzyme, BCR-Abl remains activated and cells keep reproducing. Imatinib blocks this BCR-Abl enzyme, stops the phosphorylation process, and abnormal cell growth.

The diagnosis of an early symmetrical inflammatory arthritis could be quite challenging and sometimes it takes several weeks to months following symptom onset. Frequently the association with other diseases and the response to empirical treatment guide the diagnosis, and its prognosis varies on early institution of treatment. Polyarthritis occur in association with cancer including lung, leukemias, and myelodysplastic syndromes. Hypertrophic osteoarthropathy is related to lung cancer while a symmetric or migratory polyarthritis/arthritis have been well-described on acute leukemias especially in kids. The pain in leukemic arthritis is usually severe and unresponsive to antirheumatic medication [8]. Inflammatory polyarthritis, monoarticular arthritis, polymyalgia rheumatica, and relapsing polychondritis had been reported in myelodysplastic syndromes [9]. Symmetric polyarthritis affecting the wrists and small joints of the hands, mimicking rheumatoid arthritis (RA), is a relatively rare presentation of paraneoplastic arthritis [9]. Various arthralgias and arthritis may arise as the result of treatment of malignant disease [10].

Our 28-year-old male with acute rhabdomyolysis and inflammatory polyarthritis is the first case described as initial presentation of De novo CML. Recently, a third case of Imatinib-induced acute rhabdomyolysis in CML was described in the English literature [11]. This relationship might result circumstantial. It is reasonable to consider that acute rhabdomyolysis could be a rare initial presentation of CML, instead of establishing a cause and effect relation between Imatinib and rhabdomyolysis, respectively as concluded by the Naranjo algorithm [11].

Myalgia is described as a common side effect in those treated with the first generation TKI's, however acute rhabdomyolysis is considered extremely rare. In fact, rhabdomyolysis did not occurred during the clinical trial conducted for Imatinib approval. Because tyrosine kinases participate in diverse signaling pathways, these enzymes might participate as well in the regulation of signal transduction in smooth muscle causing muscle spasm and potentially a leak of creatine kinase in CML patients [12]. It is unclear if the continuous activation of tyrosine kinase by the BCR-Abl plays an important role in the pathogenesis of patients with acute rhabdomyolysis.

Our patient was successfully treated with steroids and responded impressively well to both, his myalgias and polyarthritis. In contrast, the 28 year-old patient opted for the second generation TKI Nilotinib in ordered to avoid further episodes of rhabdomyolysis. Nilotinib also targets BCR-ABL kinase, c-KIT and platelet derived growth factor receptor (PDGFR). It is mainly used for Imatinib-resistant CML, however has been approved as a first line agent with similar efficacy. In the randomized trial in patients with newly diagnosed Ph+ CML receiving Imatinib vs. Nilotinib, non-hematologic side effects such as myalgias and arthralgias were reported at a similar rate. Nilotinib caused 35% less muscle spasm than Imatinib.

Conclusion

An acute inflammatory process manifested as acute myositis and polyarthrititis preceded the diagnosis of CML. It is reasonable to consider that acute rhabdomyolysis could be a rare initial presentation of CML instead of a chemotherapy-related myopathy. The inflammatory polyarthrititis could have been related to acute crystal arthritis, insult that responded well to steroids. The association between rhabdomyolysis and a De Novo diagnosis of CML should prompt reconsideration of its treatment. The avoidance of Imatinib as a first line therapy agent and possibly the inclusion of creatine kinase as screening tool in the same individuals could be of clinical relevance in CML.

References

1. Fader S, Talpaz M, Estrov Z, O'Brien S, Kurzrock R, et al. (1999) The biology of chronic myeloid leukemia. *N Engl J Med* 341: 164-172.
2. Savage DG, Szydlo RM, Goldman JM (1997) Clinical features at diagnosis in 430 patients with chronic myeloid leukaemia seen at a referral centre over a 16-year period. *Br J Haematol* 96: 111-116.
3. Barnes BE, Mawr B (1976) Dermatomyositis and malignancy. A review of the literature. *Ann Intern Med* 84: 68-76.
4. Casciola-Rosen L, Nagaraju K, Plotz P, Wang K, Levine S, et al. (2005) Enhanced autoantigen expression in regenerating muscle cells in idiopathic inflammatory myopathy. *J Exp Med* 201: 591-601.
5. Buchbinder R, Forbes A, Hall S, Dennett X, Giles G (2001) Incidence of malignant disease in biopsy-proven inflammatory myopathy. A population-based cohort study. *Ann Intern Med* 134: 1087-1095.
6. Manchul LA, Jin A, Pritchard KI, Tenenbaum J, Boyd NF, et al. (1985) The frequency of malignant neoplasms in patients with polymyositis-dermatomyositis. A controlled study. *Arch Intern Med* 145: 1835-1839.
7. Whitmore SE, Rosenshein NB, Provost TT (1994) Ovarian cancer in patients with dermatomyositis. *Medicine (Baltimore)* 73: 153-160.
8. Ehrenfeld M, Gur H, Shoenfeld Y (1999) Rheumatologic features of hematologic disorders. *Curr Opin Rheumatol* 11: 62-67.
9. Morel J, Deschamps V, Toussiroit E, Pertuiset E, Sordet C, et al. (2008) Characteristics and survival of 26 patients with paraneoplastic arthritis. *Ann Rheum Dis* 67: 244-247.
10. Loprinzi CL, Duffy J, Ingle JN (1993) Postchemotherapy rheumatism. *J Clin Oncol* 11: 768-770.
11. Malkan UY, Gunes G, Etgul S, Aslan T, Balaban S, et al. (2015) Management of De Novo CML and Imatinib-Induced Acute Rhabdomyolysis With the Second-Generation TKI, Dasatinib. *Ann Pharmacother* 49: 740-742.
12. Di Salvo J, Steusloff A, Semenchuk L, Satoh S, Kolquist K, et al. (1993) Tyrosine kinase inhibitors suppress agonist-induced contraction in smooth muscle. *Biochem Biophys Res Commun* 190: 968-974.