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Case Report

Acute myolysis in patients on tyrosine kinase inhibitor therapy for chronic myeloid leukemia

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Abstract: Patients on tyrosine kinase inhibitor therapy for chronic myeloid leukemia are often found to have elevated creatinine kinase levels on routine bloodwork and are asymptomatic. Here we report 4 cases of significant acute symptomatic jumps in levels with associated rhabdomyolysis that resolved with drug cessation. Etiology of the acute jumps is not known and this finding does not appear to be related to any one specific tyrosine kinase inhibitor, as 4 different tyrosine kinases were involved.

Keywords: Chronic myeloid leukemia, tyrosine kinase inhibitor, myolysis

Introduction

The past quarter century has seen the amazing change in the outcome of chronic myeloid leukemia (CML) from a near fatal disease unless stem cell transplanted to a chronic or even curable disease with near normal survival [1]. Tyrosine kinase inhibitor (TKI) therapy has become the standard of care with a number of drugs with different characteristics available [2]. Patients may now face side effect with long term use of a drug that may be chronic or appear later in therapy [3]. An early acute side effect that was noted with the earliest imatinib studies and then with other drugs to a lesser extent was muscle aches. An attempt to correlate this to elevations in creatinine kinase (CK or CPK) revealed that some patients with muscles aches had no elevation and some patients with no aches did. In fact, the CK elevation was not an uncommon finding [4]. Usually the elevation was not great, around twice the upper limited of normal, and had no cardiac implications or elevations in ESR or myeglobinuria. No long term sequelae were observed, even with continuing the effective CML therapy. In some cases, acute significant elevations that could be symptomatic could occur, often when certain statins or other drugs were added or with aggressive physical work or exercise, especially if protein supplements were added. Again no myoglobinuria suggesting rhabdomyolysis, or ESR elevations were observed [5]. The instigating event could be well established and the problem resolved quickly with holding the drugs for a week or two. A drug switch would often be all that is necessary.

CML is diagnosed by characteristic morphology on blood film and bone and with the specific Philadelphia-positive chromosome and/or the bcr:abl1 gene rearrangement. Treatment involves the use of TKIs of which there are now more than six on the market and survival in compliant patients, is essentially that of age-matched controls. Roughly a third of patients may actually be able to discontinue therapy (treatment-free remission or TFR), with the rest remaining on life-long therapy.

In addition, a musculoskeletal TKI withdrawal syndrome has been described that develops a month or two after DKI discontinuation, usually resolves by six months without intervention, but sometimes requires the use of pain/anti-inflammatory medications, rarely restarting the TKI, and even more rarely does not resolve [6]. In the latter case, investigation for other rheumatological conditions should be initiated.

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In all cases, the cause of the elevation and symptoms cannot be identified. This issue is not specific drug related, can be quite significant and debilitating, but resolves quickly on holding the drug. A switch in the drug being used maintained the CML therapy efficacy without recurrence of the symptoms. Here we report four cases involving four of the first-line approved CML TKI medications as examples and describe the management. In none of these cases was there an identified etiology.

Case 1

58 year old woman with no co-morbidities and with low Sokal chronic phase CML, diagnosed with standard bloodwork, bone marrow, cytogenetics and molecular testing, and treated with 400 mg imatinib daily for 5 years with a stable 4.3-log (0.01% IS) response, presents with severe muscle pain. Examination positive for muscle tenderness only. Baseline CK stable at 1.4 times ULN. On this occasion CK 21 times ULN. Liver enzymes, troponin, ESR all normal. Urine negative for myeglobin. Imatinib was held with resolution of symptoms within 4 days. Elected treatment-free remission option and has been successful.

Case 2

32 year old man with no co-morbidities and with low Sokal chronic phase CML diagnosed with standard bloodwork, bone marrow, cytogenetics and molecular testing, and treated with 400 mg imatinib daily for 2 years with a stable 3.8-log reduction (0.02%) response, presents with severe muscle pain. Examination remarkable for diffuse muscle tenderness. Baseline CK stable at 2.1 times ULN. On this occasion CK 8 times ULN. Liver enzymes, troponin, ESR all normal. Urine negative for myoglobin. Imatinib held and symptoms resolved within 10 days. Started on 50 mg dasatinib daily and CK stable at 1.4 times ULN. No loss of molecular response. Within 4 months, recurrence of musculoskeletal pain. Work up again unremarkable. CK now 7 times ULN. Dasatinib held and symptoms resolved in 5 days. Started on 450 mg nilotinib daily with no loss of response and no symptoms. Stable now for 2 and ½ years. Nilotinib dose now reduced to 300 mg daily.

Case 3

49 year old man with hypertension and intermediate Sokal chronic phase CML, diagnosed with standard bloodwork, bone marrow, cytogenetics and molecular testing, and treated with dasatinib dose reduced to 50 mg daily, presents with pleural effusions which are recurrent over 3 years. Molecular response was a stable deep molecular response (DMR, 4.5 log or 0.0032% IS or better). CK remained within normal limits. Dasatinib held and switched to 300 mg boutinib daily for 3 years with ongoing stable DMR (no disease detectable with 4.5 log sensitive assay) presents with muscle pain while on a cruise. Work up unremarkable except CK elevated to 6 times ULN. Mild transaminitis (ALT, AST both less than twice ULN), ESR, troponin normal. Urine negative for myoglobin. Bosutinb held and symptoms resolved within 6 days. CK normalized. Transaminases normalized off alcohol. Elected treatment free attempt and this remains successful at 1 and ½ years.

Case 4

64 year old man with no co-morbidities and low Sokal chronic phase CML, diagnosed with standard bloodwork, bone marrow, cytogenetics and molecular testing originally treated with imatinib for 9 months which was discontinued because of inadequate response. Switched to nilotinib, originally at 400 mg BID an attained a stable 3.6 log (0.04% IS) response for nearly 11 years. Nilotinib dose had been tapered to 400 mg daily with no loss of response. CK stably elevated at 1.8 times ULN. Presents with 7 day history of severe muscle pain. Exam remarkable for diffuse muscle tenderness. CK elevated to 11 times ULN. Transaminases, troponin, ESR all normal. Urine negative for myoglobin. Nilotinib held and symptoms resolved in 12 days. CK returned to normal levels. Elected to go back on imatinib at 300 mg daily and molecular response stable, CK normal now for 2 years.

Discussion

Non-inflammatory myositis is an uncommon scenario, but here we have 5 episodes in 4 patients on 4 different TKIs for CML. No cases

with newer drugs have been seen or reported. It is highly unlikely that the TKI was responsible for these acute myositis episodes as the patients had all been on therapy for years with no such symptoms. Whether the TKI was responsible for the susceptibility to an unknown insult, is again unknown. Despite this, prompt suspension of the different TKI therapies resulted in improvement and in fact normalization of symptoms suggesting some kind of relationship. Without any identified cause and effect or relationship to any specific drug, there can still be lessons to be learned however from these acute events.

1. Elevated CK can occur with TKI CML therapy. It is usually not significant, has no apparent long term implications and can occur at least with all first and second generation TKIs. It should be routinely monitored.

2. There appears to be no real correlations to low grade muscle pain and CK elevation.

3. An acute occurrence of severe muscle pain should be investigated with CK, transaminases, ESR, and urine for myoglobin plus any other tests suggested by history and exam.

4. Rhabdomyolysis does not seem to be associated with this phenomenon.

5. With no other etiologies and non-inflammatory in nature, TKI should be held and resolution should be seen promptly.

6. Acute significant elevations in CK on routine blood tests even without symptoms, should initiate questioning on new drugs, supplements, excessive exercise, and protein supplement usage. Again, holding these should result in resolution if responsible. Additional tests can be considered.

7. With resolution of symptoms, options can include a switch in TKI as the event is idiosyncratic, or a treatment free remission attempt if appropriate. Restarting the same TKI should be done with informed consent, caution, and close observation, and perhaps is the less predictable choice.

Being sure this is a real myositis or not, if symptoms do not respond to holding the drug is then the question [7]. Rheumatologiclal disorders have been found to be associated with myeloproliferative neoplasms [8] and with cancer immunotherapy [9], but again an acute onset in a symptomless patient suggests and alternative etiology. Paraneoplastic rheumatological conditions are also known, but usually not with myeloid malignancies [10]. In addition, some infections can be associated with myositis.

Myositis if the cause is uncertain, should be worked up with the appropriate consultation. Newer blood tests [11] and even biopsy [12] may lead to a diagnosis. Of course it should be remembered that in a disease where the median age of diagnosis in the western world is around 65 years old, other diseases such as osteoarthritis and polymyalgia, to name just a couple can develop, totally unrelated to the CML. The primary response to this diagnosis is to stop the TKI and see if the symptoms and bloodwork resolve. As quoted by Araceli Jasso - “You know you’re getting old when everything hurts, and what doesn’t hurt, doesn’t work”.

Disclosure of conflict of interest

JH has had research funding and served on advisory boards for Novartis, BMS, Pfizer, Takeda (Ariad).

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References

[1] Bower H, Björkholm M, Dickman PW, Höglund M, Lambert PC and Andersson TM. Life expectancy of patients with chronic myeloid leukemia approaches the life expectancy of the general population. J Clin Oncol 2016; 34: 2851-7.

[2] Jabbour E and Kantarjian H. Chronic myeloid leukemia: 2025 update on diagnosis, therapy, and monitoring. Am J Hematol 2024; 99: 2191-2212.

[3] Lipton JH, Brümmendorf TH, Gambacorti-Passerini C, Garcia-Gutiérrez V, Deininger MW and Cortes JE. Long-term safety review of tyrosine kinase inhibitors in chronic myeloid leukemia - What to look for when treatment-free remission is not an option. Blood Rev 2022; 56: 100968.

[4] Bankar A and Lipton JH. Association of creatine kinase elevation with clinical outcomes in chronic myeloid leukemia: a retrospective

cohort study. Leuk Lymphoma 2022; 63: 179-188.
[5] Zhang H and To KKW. Serum creatine kinase elevation following tyrosine kinase inhibitor treatment in cancer patients: symptoms, mechanism, and clinical management. Clin Transl Sci 2024; 17: e70053.
[6] Richter J, Soderlund S, Lubking A, Dreimane A, Lotfi K, Markevam B, Sjalander A, Saussele S, Olsson-Stromberg U and Stenke L. Musculoskeletal pain in patients with chronic myeloid leukemia after discontinuation of imatinib: a tyrosine kinase inhibitor withdrawal syndrome? J Clin Oncol 2014; 32: 2821-3.
[7] Bhai SF, Dimachkie MM and de Visser M. Is it really myositis? Mimics and pitfalls. Best Pract Res Clin Rheumatol 2022; 36: 101764.
[8] Sasi S, Mohamed M, Chitrambika P and Yassin M. Myasthenia gravis and myeloproliferative neoplasms - mere association or paraneoplastic neurologic syndrome: a mini-review. Acta Biomed 2022; 92: e2021437.
[9] Roberts J, Ennis D, Hudson M, Ye C, Saltman A, Himmel M, Rottapel R, Pope J, Hoa S, Tisseverasinghe A, Fifi-Mah A, Maltez N and Jamal S. Rheumatic immune-related adverse events associated with cancer immunotherapy: a nationwide multi-center cohort. Autoimmun Rev 2020; 19: 102595.
[10] Mammen AL. Paraneoplastic myopathies. Handb Clin Neurol 2024; 200: 327-332.
[11] Harvey GR, MacFadyen C and Tansley SL. Newer autoantibodies and laboratory assessments in myositis. Curr Rheumatol Rep 2024; 27: 5.
[12] Hofer M and Brady S. Clinicopathological collaboration in adult muscle disease: a pragmatic pathway to approach diagnostic dilemmas. Pathology 2025; 57: 220-229.