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CLINICAL VIGNETTE

Chronic Myeloid Leukemia Presenting with Thrombocytosis and the Acquired von Willebrand Syndrome

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Case Description

A 56-year-old man presented to primary care at the behest of his dentist and oral surgeon. The patient was obese with a prior diagnosis of type 2 diabetes mellitus but had no routine medical care for the past 5 years. Approximately 6 months prior he developed a nodule arising from the right mandibular gingival mucosa. CT imaging showed a mildly expansile cystic lesion involving the right body of the mandible. Lab testing was notable for a leukocytosis to 15,000 WBC/µL as well as a platelet count of 1,363,000 per µL. The findings prompted his dental providers to refer the patient for medical evaluation, particularly out of concern for an advanced infection.

The patient reported no pain, tenderness, or drainage at the site of the growth. He did not have fevers or chills and denied any other localizing infectious symptoms. He had practiced appropriate oral hygiene in the years preceding the development of this growth, but recently noticed gingival bleeding while brushing his teeth. He was afebrile with a normal heart rate and blood pressure. On exam he had fair dentition with a 1 cm nodule below the bottom right premolar tooth. The nodule was firm but depressible and was not tender or inflamed. There was no lymphadenopathy of the head or neck and there were no murmurs or other abnormal heart sounds on auscultation.

While his leukocytosis and profound thrombocytosis suggested an infectious process underlying the cystic growth, the history and exam did not seem consistent. As the patient was afebrile and hemodynamically stable, antibiotics were deferred and alternative explanations for his hematologic abnormalities were explored. The erythrocyte sedimentation rate was within normal limits suggesting a non-inflammatory process. Given the thrombocytosis, mutational analysis of the peripheral blood for JAK2 V617F, CALR, and MPL mutations was performed which returned negative. As the differential for the white blood cell count returned with an absolute neutrophilia, eosinophilia, and basophilia, a serum BCR-ABL PCR was collected and returned positive indicating a diagnosis of chronic myeloid leukemia.

Due to the complaint of mucosal bleeding, a PT and PTT were also checked and were notable for prolongation of the PTT to 51.3 seconds. This finding in the context of the newly diagnosed leukemia suggested acquired von Willebrand syndrome prompting additional testing including a ristocetin cofactor level which was abnormally low. The patient was referred to hematology and was confirmed to have chronic myeloid leukemia with severe thrombocytosis resulting in the acquired von Willebrand syndrome.

It remained unclear whether the oral lesion was related to this diagnosis and so a biopsy was recommended but had to delayed due to excessive bleeding risk related to the acquired Von Willebrand syndrome. The patient was started on the oral tyrosine kinase inhibitor imatinib and within 2 months his white blood cell and platelet counts normalized along with his PTT and ristocetin cofactor level. At this point he underwent an uncomplicated biopsy of the oral lesion which demonstrated a benign odontogenic keratocyst thought to be incidental and unrelated to the leukemia.

Discussion

Chronic myeloid leukemia (CML) is a type of myeloproliferative neoplasm resulting in dysregulated proliferation of granulocytes in the bone marrow. It accounts for 15 percent of leukemias in the adult population and typically develops between the ages of 45 to 55.[1] While a variety of genetic abnormalities may be found in CML, the defining chromosomal translocation seen in all cases results in the "Philadelphia chromosome" containing the BCR-ABL1 fusion gene. The protein product of this fusion gene is composed of a portion of the ABL1 tyrosine kinase, which normally functions to promote cellular replication. Unadulterated, the entire ABL1 enzyme is carefully regulated by the cell. However, when partially replaced by a fused BCR protein, cell replication cannot be suppressed leading to unbridled proliferation of myeloid cell types including granulocyte and platelet lineages.[2]

CML classically takes a triphasic clinical course beginning with a chronic phase in which well differentiated mature neutrophils are produced in high amounts. This phase is typically followed by an accelerated phase associated with increasing counts of myeloid cells containing additional cytogenetic abnormalities along with a higher number of blasts in the circulation and bone marrow. Untreated patients will then subsequently enter a terminal blast phase characterized by very high counts of blasts in the peripheral blood, bone marrow, and potentially other tissues infiltrated by these cells.[3]

As was the case for this patient, most individuals with CML are diagnosed in the chronic phase. While many patients will be asymptomatic at the time of diagnosis, patients can also present with constitutional symptoms including fatigue, weight loss, and night sweats. The complete blood count will typically show a leukocytosis with increased counts of mature neutrophils, eosinophils, and basophils. Though not always seen, an increased platelet count is not uncommon. Patients in the blast phase are usually symptomatic and ill-appearing with constitutional symptoms, excessive clotting or bleeding, and symptoms related to extramedullary proliferation or infiltration into other tissues.[3] While it was possible that the oral cystic lesion represented extramedullary growth, this was unlikely in a patient in the chronic phase of CML and biopsy confirmed this suspicion.

This patient did not present with overt constitutional symptoms and his white blood cell count was characteristically elevated as in other cases of CML. While elevated platelet counts are typically associated with a serious infectious or inflammatory process, the impressive thrombocytosis in the absence of such a pathology prompted the primary care physician to search for an alternate explanation. The myeloproliferative neoplasm classically associated with elevated platelet counts is essential thrombocythemia, commonly caused by the JAK2 V617F mutation.[4] When clinical suspicion for essential thrombocythemia is present, genetic mutational analysis on the peripheral blood can be done to search for the presence of this mutation. If negative and clinical suspicion remains, testing for less common mutations such as the CALR or MPL mutations may be performed.[4] When these tests returned negative in this patient, the presence of a leukocytosis with increased eosinophil and basophil counts led to BCR-ABL PCR testing of the peripheral blood which identified the presence of this abnormal genetic rearrangement. While this can be sufficient to make the diagnosis, a bone marrow biopsy may be performed for complete staging as presence of a high blast burden or other features may contribute to prognostication and treatment planning.[4]

Left untreated, patients with chronic phase CML will progress to the blast phase within three to five years.[1] Prior to the development of current therapeutics, the median survival of patients who reached blast phase was only three to six months. Tyrosine kinase inhibitors (TKIs) which directly target the BCR-ABL1 protein have revolutionized CML management by improving outcomes without the toxicities seen with aggressive cytotoxic regimens or interferon treatments used in the past for this entity. With TKIs, the life expectancy of patients in the chronic phase approaches that of the general population and the median survival of patients in the blast phase has increased to 12 months.[3] Of the prior treatment options for CML, allogenic hematopoietic stem cell transplant remains relevant as the only potentially curative option though it comes with added treatment toxicity and a relatively high risk of early mortality. The success of original TKIs like imatinib and newer generations of these agents capable of bypassing leukemic resistance has led to their promotion as first line treatment in nearly all cases of CML.[2] This patient was started on imatinib, the first oral tyrosine kinase inhibitor developed, which resulted in a decline in BCR-ABL transcript levels along with normalization of his blood counts and coagulation times.

This patient's presentation was notable for gingival bleeding in the context of extreme thrombocytosis and prolonged PTT. These findings suggested the acquired von Willebrand syndrome. As opposed to the genetic von Willebrand disease caused by an inherited germline mutation, the acquired syndrome is due to decreased activity of the von Willebrand factor related to a deficiency or abnormal function caused by some underlying pathology. The von Willebrand factor (vWF) is a large glycoprotein that which plays a critical role in hemostasis by binding to and linking platelets with subendothelial structures at sites of vascular injury. When platelet counts are extremely high, the platelets will adsorb circulating vWF protein removing it from circulation and accelerating its clearance through proteolytic cleavage.[5] Since vWF protein also stabilizes factor VIII, depleted levels of vWF may lead to PTT prolongation. While thrombocytosis does generally increase the risk of thrombosis, the concomitant quantitative decrement of vWF seen in extreme cases may paradoxically increase the risk of bleeding. The acquired von Willebrand syndrome can be confirmed by checking the ristocetin cofactor activity, a standardized functional assessment of vWF activity.[5] The ristocetin cofactor activity level was low in this patient and normalized alongside the platelet count and PTT after initiation of imatinib. This allowed for the biopsy of the oral cystic lesion under safer conditions with minimal risk of excessive bleeding.

Conclusion

When evaluating abnormal findings on even routine lab tests including a complete blood count, the clinical history, examination, and additional lab findings must be considered and synthesized to arrive at the correct diagnosis. While elevated white blood cell counts are commonly seen with infections, when accompanied by other cell line abnormalities, other entities should enter the differential diagnosis. While CML remains a relatively rare cause of leukocytosis in the general ambulatory adult population, it should also be considered in these cases. Furthermore, elevated platelet counts with prolonged coagulation times and evidence of bleeding diathesis suggest the acquired von Willebrand syndrome and warrants further careful evaluation.

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