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The first concurrent diagnosis of acute symptomatic Babesiosis and chronic myeloid leukemia in a healthy young adult

TO THE EDITOR: Babesiosis is an infectious disease caused by hemoparasite *Babesia* and transmitted by certain ticks or transfusions. Few *Babesia* species (*B. microti*, *B. venatorum*, *B. duncani*, *B. divergens*) are associated with human infection. Although many patients are asymptomatic and recover spontaneously, the infection can be persistent, refractory, and life-threatening in immunosuppressed hosts, especially those receiving chemotherapy or immunosuppression, transplant, or splenectomy [1-4].

We report the case of a healthy young patient who was concurrently diagnosed with acute symptomatic Babesia infection and chronic myeloid leukemia (CML). A 23-year-old man, living in New Hampshire, presented with fever, fatigue, myalgia, and arthralgia for 2 weeks. The patient had no history of any malignancy, transfusion, chemotherapy, or immunosuppression. He had no recent travels or did not recall any tick exposure.

At admission, the patient complained of sweating, body aches, and headache. Physical examination was unremarkable except fever (40°C). Blood tests showed left-shifted neutrophilic leukocytosis (white blood cell: $89.6 \times 10^3/\mu\text{L}$; myelocyte 17%, metamyelocyte 8%, band/segmented neutrophil 69%, lymphocyte 3%, monocyte 3%) and normocytic anemia (hemoglobin 9.3 g/dL; mean corpuscular volume 84.5 fL). Serum liver function tests were normal except increased lactate dehydrogenase (654 U/L). Abdominal computed tomography scan showed splenomegaly. After specimen collection for blood culture and serologic tests to rule out the infectious etiology, the patient was started on general antimicrobial therapy. The blood culture for aerobic and anaerobic microorganisms was negative. Serologic tests showed positive *B. microti* immunoglobulin M (IgM; >1:320; reference range, <1:20) and cytomegalovirus (CMV) IgM (2.57; reference range, <0.89). Human immunodeficiency virus screening, Lyme IgM/IgG, Epstein-Barr virus anti-viral capsid antigen IgM, *B. microti* IgG, and *Anaplasma phagocytophilum* IgM/IgG antibodies were negative. Monospot test result was negative.

Given the presence of marked left-shifted neutrophilic leukocytosis in peripheral blood (PB), bone marrow (BM) biopsy was performed to rule out leukemoid reaction or underlying myeloid neoplasm. BM biopsy showed hypercellularity (100%) and left-shifted granulocytic hyperplasia. Megakaryocytes were slightly increased with many having small hypolobated (dwarf) forms (Fig. 1A, B). Sea-blue histiocytes were increased. However, there were no increased blasts or significant dysplasia. Flow cytometric analysis showed no evidence of a lymphoma or leukemia. Results

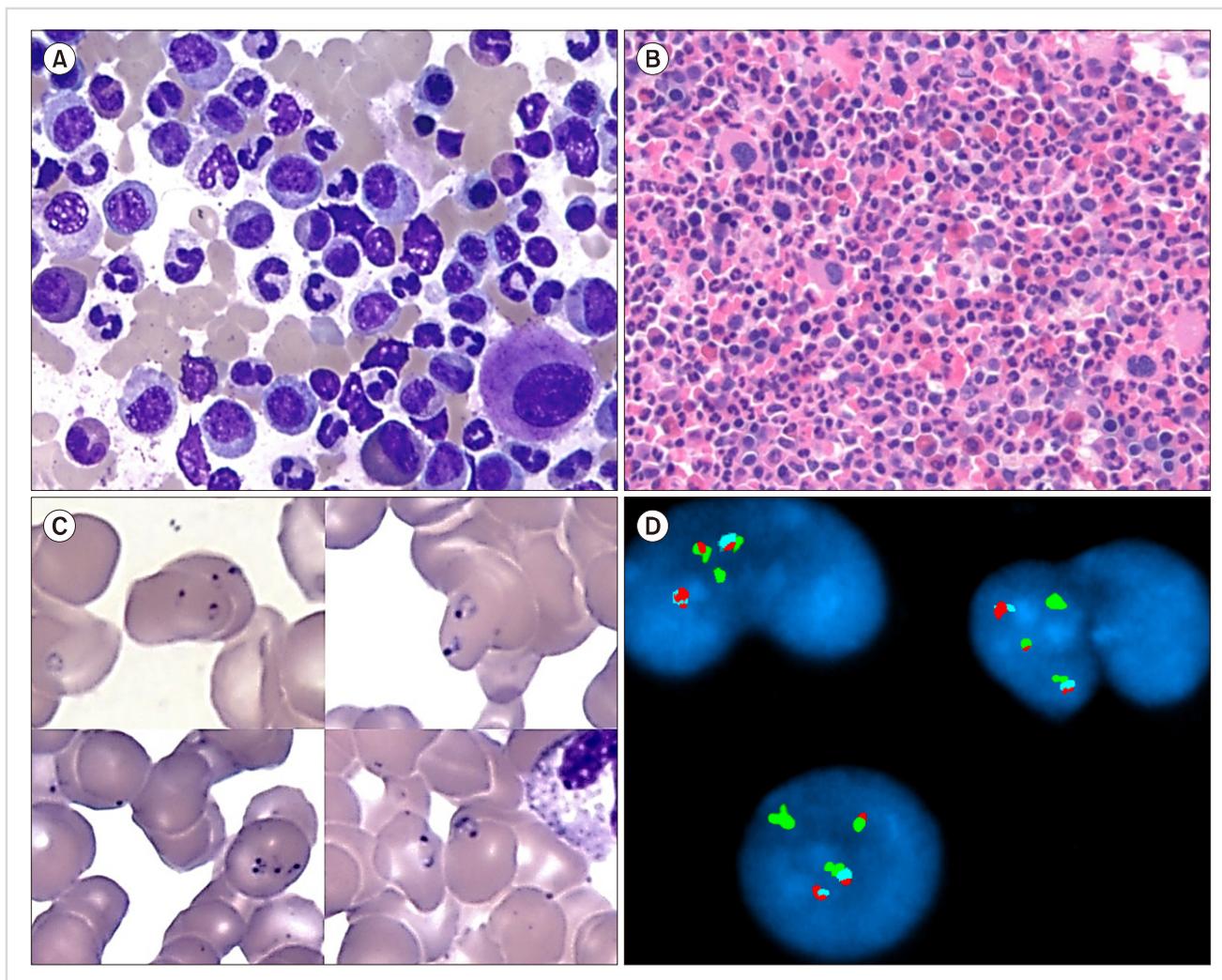


Fig. 1. Bone marrow (BM) histopathologic and cytogenetic findings at diagnosis. **(A, B)** BM aspirate and biopsy showed left-shifted granulocytic hyperplasia with a high myeloid:erythroid ratio and megakaryocytes with small hypolobated (dwarf) forms (**A**: Wright-Giemsa stain, $\times 1,000$, **B**: hematoxylin and eosin stain, $\times 400$). **(C)** The composite pictures from the aspirate smears showed small single or multiple ring-form organisms within the erythrocytes. One of the erythrocytes in the left lower part showed the stage occurring after the breakdown of the classic tetrad (“Maltese cross”) (Wright-Giemsa stain, $\times 1,000$). **(D)** Fluorescent in-situ hybridization in BM specimen using tri-color dual fusion probes (BCR/ABL1/ASS1) demonstrated BCR/ABL1 translocation (red-green fusion) in 3 interphase cells. ABL1 and ASS1 probes in chromosome 9q34 region and BCR probe in chromosome 22q11.2 region showed red, aqua, and green signals, respectively (Abbott Molecular, Abbott Park, IL).

of immunohistochemistry for CMV was negative on the core biopsy. Interestingly, BM aspirate smears showed many small single or multiple ring-form organisms within the erythrocytes, with occasional 4 rings representing the stages after breakdown of the classic tetrad (“Maltese cross”) (Fig. 1C). No other cellular inclusions or granulomatous lesions were noted. Acute Babesia infection was diagnosed in combination with elevated *B. microti* IgM by immunoassay. Fluorescent in situ hybridization demonstrated BCR/ABL1 fusion in 187/200 (93.5%) of interphase cells (Fig. 1D). Karyotype showed 46,XY,t(9;22)(q34;q11.2) [20]. Real-time quantitative polymerase chain reaction (PCR) showed p210 BCR/ABL1 fusion transcript (e13a2 and e14a2; International Scale 60.8%) in PB. Therefore, diagnosis of CML in chronic phase was rendered. After diagnosis of Babesiosis, the patient

received antimicrobial therapies (atovaquone, azithromycin, clindamycin) for 7 days and showed a good response with no intraerythrocytic Babesia in PB smears. Therapy of tyrosine kinase inhibitors (TKIs) and potential BM transplant were discussed.

The Northeast and Upper Midwest part of the US is endemic for Babesiosis, and the majority of infection is caused by *B. microti*, transmitted by the tick, *Ixodes scapularis*, which also causes Lyme disease and anaplasmosis. Elderly, immunocompromised, or asplenic patients are at high risk of persistent Babesia infection [4]. Acquired Babesiosis after transfusion of blood products from asymptomatic donors has been recently increasing [5]. The clinical manifestations of Babesiosis, which infects erythrocytes, can range from asymptomatic disease to mild/moderate to fatal illness.

Mild/moderate illness can manifest as non-specific flu-like symptoms (chills, sweats, anorexia, headache, myalgia, non-productive cough, arthralgia). Physical examination can include fever or splenomegaly and hepatomegaly occasionally. Severe Babesiosis can cause severe hemolytic anemia, disseminated intravascular coagulation, acute renal failure, and multisystem organ failure, which is threatening in immunosuppressed or asplenic patients [2, 3, 6].

The patient likely had an environmental source of infection since he never received transfusions or immunosuppressive therapy, was physically active, and lived in New Hampshire, an endemic area for *Babesia*. When tick exposure is suspected, other infections such as Lyme disease/borreliosis, ehrlichiosis, and anaplasmosis should be screened to rule out co-infection. Up to 50% of Babesiosis patients have a history of Lyme disease or positive serologic results for antibodies against *Borrelia burgdorferi* [6].

The diagnosis of Babesiosis is made after identifying small single or multiple ring forms or the pathognomonic "Maltese cross" or tetrads of *Babesia* organisms within/outside erythrocytes on thin blood smears [3, 6]. The exclusion of other parasites forming intraerythrocytic ring forms should be taken into consideration as differential diagnosis. PCR and serologic studies support the diagnosis and help in monitoring the therapeutic response. As shown in this case, antimicrobial therapy with either quinine and clindamycin or atovaquone and azithromycin for 7–10 days is effective for mild/moderate Babesiosis. However, the therapy can be prolonged for at least 6 weeks in immunocompromised patients with additional transfusions [5, 7].

In this young patient, BM biopsy and genetic studies revealed chronic phase of CML. The median age of CML diagnosis is approximately 67 years. CML diagnosed at younger ages (15–29 yr) is referred to as adolescents and young adults (AYA) and represents a small distinct group, ranging from 8% to 13% of all CML patients [8, 9]. Studies of AYA patients with CML demonstrated different biology and prognosis compared with older patients [8–10]. AYA patients show higher leukocyte count, incidence of splenomegaly, higher PB blasts percent, and lower hemoglobin levels than older patients. Splenomegaly in CML is attributed to the expansion of myeloid cells and immune-inflammatory response. The spleen sequesters erythrocytes infected with *Babesia* or platelets by macrophages. In immunocompetent patients with some degree of higher splenomegaly, like our patient, *Babesia* infection can cause spontaneous splenic rupture or infarction related to splenic erythrophagocytosis [3, 8].

TKI therapy has drastically improved the outcome of CML patients. Survival outcomes seem to be unaffected by age. However, AYA patients show higher progression rate to aggressive or blastic phase and inferior response to TKI therapy than older patients [8, 9].

To the best of our knowledge, this is the first case of concurrent diagnosis of acute symptomatic Babesiosis and CML in a young immunocompetent adult.

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No potential conflicts of interest relevant to this article were reported.

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Evaluation of thrombocytopenia in the hematology clinic: a case series from a large tertiary care center

TO THE EDITOR: Thrombocytopenia is a common hematologic condition with multiple causes ranging from benign to potentially life-threatening disorders. Few evidence-based recommendations are available regarding a specific diagnostic approach to thrombocytopenia in the hematology clinic [1-3]. Although a limited test repertoire may be adequate in many cases, more extensive testing may be warranted in others. We sought to analyze the utilization and impact of different laboratory evaluation strategies in the initial workup of thrombocytopenia.

We included 68 patients seen at our outpatient hematology clinic between 2010 and 2015 for an initial workup of thrombocytopenia of unclear etiology (Table 1). The median age at thrombocytopenia diagnosis was 60 (range, 17-90) years, and the majority of patients (64.7%) were male. The median platelet count at diagnosis was 91 (range, 3-146) ×

10⁹/L: 30 patients (44.1%) with a platelet count of 100-146 × 10⁹/L, 26 (38.2%) with a platelet count of 50-100 × 10⁹/L, and 12 (17.6%) with a platelet count of <50 × 10⁹/L.

Although 37 patients (54.4%) and 27 patients (39.7%) underwent evaluation for autoimmune causes and infectious diseases, respectively, only the following few test results were positive: anti-glycoprotein platelet antibodies (N=2; although routine use of this testing is not recommended [4]), anti-nuclear antibodies (N=4), elevated rheumatoid factor level (N=1), and anti-IgM Epstein-Barr virus antibody (N=1). None had hepatitis B or C, or HIV despite routine use of these tests. Bone marrow biopsies performed on 16 patients (23.5%) revealed abnormalities in 2 patients (both with coexisting anemia and leukopenia at the time of the thrombocytopenia workup): one with hairy cell leukemia and one with myelodysplastic syndrome (refractory anemia with excess blasts-2).

Based on the results of these tests, 27 patients (39.7%) were diagnosed with primary immune thrombocytopenia, and 23 patients (33.8%) were diagnosed with thrombocytopenia due to possible multifactorial causes, 5 (7.4%) suspected to be due to drugs (tacrolimus, methotrexate, bosentan, amitriptyline, or adalimumab), 4 (5.9%) due to hypersplenism, 4 (5.9%) due to unclear etiology, and 2 (2.9%) due to hematologic malignancies; 1 patient (1.5%) each was diagnosed with thrombocytopenia secondary to lupus, liver cirrhosis secondary to non-alcoholic steatohepatitis associated with hypersplenism, and gestational thrombocytopenia.

Table 1. Evaluation of thrombocytopenia in the hematology clinic.

Type of workup	N (%) of patients (N=69)	Test results	
		Positive (%)	Negative (%)
Abdominal ultrasound	7 (10.3%)	3 (42.9%): chronic liver disease with hypersplenism in 2 ^{a)} and hypersplenism in 1	4 (57.1%)
Autoimmune workup	37 (54.4%)		
Anti-glycoprotein platelet antibody	33 (48.5%)	2 (6.1%)	31 (93.9%)
Antinuclear antibody	21 (31.0%)	4 (19.0%)	17 (81.0%)
Lupus anticoagulant	4 (5.9%)	0 (0%)	4 (100%)
Rheumatoid factor	13 (19.1%)	1 (7.7%)	12 (92.3%)
Bone marrow biopsy	16 (23.5%)	2 (12.5%): myelodysplastic syndrome and hairy cell leukemia	14 (87.5%)
Infectious disease evaluation	27 (39.7%)		
Cytomegalovirus	6 (8.8%)	0 (0%)	6 (100%)
Epstein-Barr virus	5 (7.4%)	1 (20%)	4 (80%)
Hepatitis A virus	2 (2.9%)	0 (0%)	2 (100%)
Hepatitis B virus	10 (14.7%)	0 (0%)	10 (100%)
Hepatitis C virus	22 (32.4%)	0 (0%)	22 (100%)
Human immunodeficiency virus	22 (32.4%)	0 (0%)	22 (100%)
<i>Helicobacter pylori</i>	4 (5.9%)	0 (0%)	4 (100%)
Peripheral blood smear	3 (63.2%)	4 (9.3%): large, elongated, well-granulated platelets (N=2); rouleaux formation; target cells; lymphocytes with circumferential hairy cytoplasmic projections	39 (90.7%)

^{a)}One of these patients with chronic liver disease also had other possible etiologies of the thrombocytopenia, including medications and possible Epstein-Barr virus reactivation, and hence was included as 1 among 23 cases with a multifactorial cause.