Patients with thrombocytopenia are often recommended to undergo a variety of tests, much of which may not be indicated and/or diagnostically helpful. In this series, we found that although a large percentage of patients underwent multiple laboratory tests and pathologic evaluation, these tests often did not offer significant insight into the etiology of the thrombocytopenia. This is congruent with results from other studies specifically focusing on bone marrow biopsies in the workup of thrombocytopenia [1, 2] and further adds to the literature with regard to autoimmune and infectious workup. Additionally, nearly half of the patients in this series had a platelet count $>100\times10^9$/L, which may in some cases be considered a normal variant [3].

In summary, evaluation of thrombocytopenia should vary based on individual patient history and risk factors rather than a one-size-fits-all testing panel. Our study was based on a small cohort of patients but is likely representative of clinical practice at many large tertiary care centers. Large-scale prospective studies may be helpful to define the optimal workup for thrombocytopenia and formulate a protocol for cost-effective workup by stratification of clinical risk factors.

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ALM and AR designed the study, performed the data collection, and analyzed the data. ALM, AR, RSG, and KKR drafted the manuscript. All authors approved the final version of the manuscript.

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Microangiopathic hemolytic anemia as initial presentation of recurrent colon cancer

TO THE EDITOR: Microangiopathic hemolytic anemia (MAHA) refers to mechanical hemolytic anemia characterized by red blood cell fragmentation or schistocytes on peripheral blood (PB) smear [1]. MAHA is observed in various conditions such as thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), disseminated intravascular coagulation (DIC), systemic infection, and immune disorders [2-4]. MAHA can also occur rarely in malignant tumors as paraneoplastic syndrome. Gastric cancer is the most frequent malignancy associated with MAHA, followed by cancers of the breast, prostate, lung and cancer of unknown origin. Colon cancer presenting with MAHA is much rarer, and only a few cases have been reported [2, 3, 5]. In most cancer-related MAHA (CR-MAHA) cases, MAHA is detected at initial diagnosis of cancer. However, in about 20% of cases, it emerges at the time of cancer recurrence, particularly in gastric and breast cancers, and usually reflects late stage of disease [5]. When MAHA presents as the first sign of recurrent malignancy, the underlying cause may not be suspected initially, leading to inappropriate management. Herein, we describe a case of relapsed colon cancer which presented no sign of recurrence except MAHA as the initial manifestation.

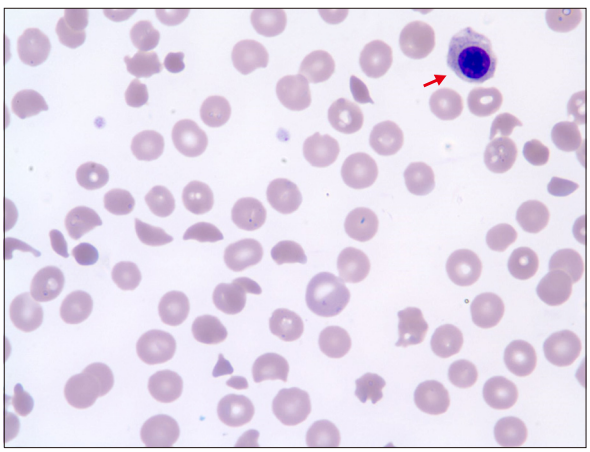

Fig. 1. Schistocytes, polychromasia and nucleated RBC (arrow) in peripheral blood (Wright stain, ×1,000).

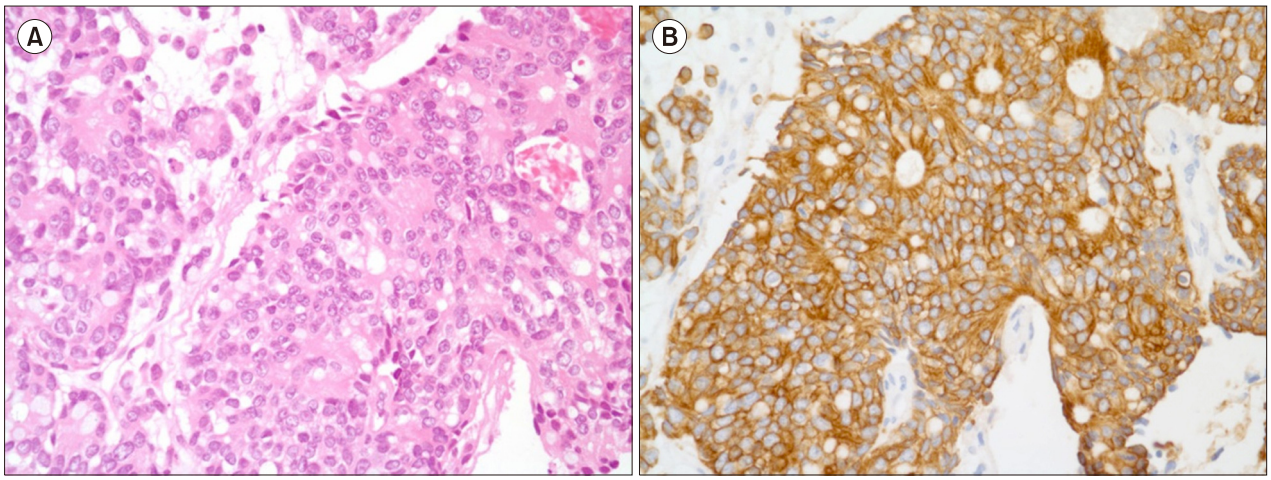

Fig. 2. Bone marrow biopsy. **(A)** Infiltration of tumor cells (H&E stain, ×400). **(B)** Tumor cells positive for CK20 (CK20 stain, ×400).

A 76-year-old woman was admitted to our hospital with ecchymosis that developed suddenly all over her body accompanied by headache. Three years ago, she was diagnosed with colon cancer and underwent hemicolectomy followed by adjuvant chemotherapy with leucovorin and 5-fluorouracil. Since then, the patient was regularly followed up. The last checkup was 7 weeks ago, and no evidence of disease recurrence was seen on abdominopelvic computed tomography (CT) scan. Blood cell counts at that time were: white blood cells (WBC), 4.88×10^9/L; hemoglobin (Hb), 11.4 g/dL; and platelets, 117×10^9/L. Chemistry results were unremarkable. Her complete blood count (CBC) on admission was as follows: WBC, 5.9×10^9/L; Hb, 6.7 g/dL; and platelets, 4×10^9/L. Other significant laboratory results included lactate dehydrogenase (LDH), 2,016 U/L [normal level (NL), 240–480 U/L]; alkaline phosphatase (ALP), 262 IU/L (NL, 35–104 IU/L); total bilirubin, 2.86 mg/dL (NL, 0.2–1.2 mg/dL) with direct bilirubin, 0.35 mg/dL (NL, 0–0.3 mg/dL); prothrombin time (PT), 18.2 s (NL, 9–13 s); activated partial thromboplastin time (aPTT), 39.0 s (NL, 25–37 s); D-dimer, 36,641 ng/mL (NL, 0–250 ng/mL); haptoglobin, 4 mg/dL (NL, 30-200 mg/dL) and a negative direct Coombs' test. PB smear showed numerous fragmented erythrocytes, polychromasia, nucleated red blood cells (RBCs) (Fig. 1), and leukoerythroblastic reaction. A diagnosis of MAHA was made on the basis of laboratory findings. Brain CT scan revealed acute subdural hemorrhage (SDH) on both fronto-parieto-temporal lobes. Abdominopelvic CT scan and whole spine X-ray showed no evidence of newly appeared distant metastasis of cancer. Urgent neurosurgery was scheduled; however, it was withheld due to low platelet count. Despite multiple blood transfusions, her blood counts did not improve. Schistocytosis and leukoerythroblastic reaction were still observed on a repeat PB smear, and values of other significant laboratory parameters such as LDH and total bilirubin continued to worsen, implying a progression of MAHA. Then, bone marrow (BM) examination was performed for the workup of MAHA and thrombocytopenia; however, BM aspirate showed no adequate particles with dry tap. While awaiting the slide preparation of the biopsy section, plasma exchange was planned with a diagnostic consideration of TTP. Unexpectedly, the biopsy section revealed diffuse infiltration of atypical mononuclear cells, suggestive of BM involvement of malignant tumor (Fig. 2A). Hence, plasma exchange was withheld. With rapidly progressive clinical course, the patient expired on the 10th day since admission. The results of immunohistochemical staining arrived a few days later, and the atypical cells were positive for CK20 stain (Fig. 2B) and negative for CK7 stain. A final diagnosis of BM metastasis of poorly differentiated adenocarcinoma clinically from colon was made.

MAHA can be seen in various diseases which share similar laboratory and clinical features. In patients with an abrupt onset of MAHA and thrombocytopenia, a diagnosis of TTP and urgent management such as plasma exchange should be preferentially considered. Because TTP is a medical emergency, complete presentation of the classic pentad of TTP including MAHA, thrombocytopenia, fever, neurological symptoms and renal disease may not be strictly required for its clinical diagnosis. CR-MAHA with no apparent systemic manifestation of malignancy may be often included in such cases. This leads to the trial of plasma exchange, which is seldom effective and may cause unnecessary risk of complication in CR-MAHA cases [6-8]. Presenting laboratory findings in this case are indicative of overt DIC, although a diagnosis of DIC should be based on both clinical and laboratory features. A close association of CR-MAHA with DIC is well described [3, 5, 6]. According to a multicenter study involving 12 cases of CR-MAHA, all cases showed severely increased D-dimer levels [2]. It was suggested that the generation of small vessel thrombi in CR-MAHA may be increased by simultaneous DIC. Extreme elevation of D-dimer, as in this case, may support disseminated malignancy rather than TTP, even though no single test can establish or exclude the diagnosis [2, 5, 7].

Although BM metastasis is commonly found in CR-MAHA, it is seldom an initial presenting feature of malignant tumor. BM metastasis from colon cancer is very rare, particularly when encountered in the absence of usual distant metastases such as liver and lungs [8-10]. Generally, BM study is not routinely considered in solid tumor workup; however, PB slide examination is performed in almost all known or suspected cancer cases as a simple screening tool. One of the well-known PB findings suggestive of BM involvement of malignancy is leukoerythroblastic reaction. Although leukoerythroblastic reaction is not specific for malignant conditions, its presence accompanied by MAHA could be a strong indicator of BM examination in cases with unexplained cytopenia [10].

Chemotherapy is the only effective treatment for CR-MAHA. Although the prognosis of CR-MAHA is generally poor, several studies reported cases of favorable response of CR-MAHA to chemotherapy [2, 4, 5]. As MAHA is not a common presenting sign of cancer recurrence, early recognition of this rare presentation and prompt investigation including BM study are essential for timely management.

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Long-term control of refractory follicular lymphoma after treatment of secondary acute promyelocytic leukemia with arsenic trioxide (As_2O_3) and all-trans retinoic acid (ATRA)

TO THE EDITOR: A 50-year-old Caucasian woman presented with gradually progressive fatigue, night sweats, and cellulitis of the lower abdominal wall in April 2000. In addition, she had morbid obesity, depression, osteoarthritis, and obstructive sleep apnea. Computerized tomography (CT) scan revealed lymphadenopathy above and below the diaphragm with moderately enlarged retroperitoneal and pelvic lymph nodes and hepatosplenomegaly. Laboratory data were unremarkable, with blood counts and serum lactate dehydrogenase levels within normal limits. CT-guided inguinal lymph node biopsy was consistent with follicular lymphoma (FL) [cluster of differentiation (CD)20 and Bcl2+]. Bone marrow biopsy revealed multifocal involvement with CD10-positive small lymphocytes distributed in the paratrabecular areas. She was diagnosed as having stage IVB FL. She was treated with 6 cycles of rituximab-cyclophosphamide, doxorubicin (Adriamycin), vincristine, and prednisone with 2 additional rituximab doses. She achieved complete remission (CR), as documented by CT scan and bone marrow examination. She then received maintenance interferon therapy for an additional 10 months and remained in CR for the next 4 years. In January 2005, a routine screening mammogram showed a 2.5-cm-sized mass in her left breast. Ultrasound-guided core needle biopsy was consistent with FL grade 2 (Fig. 1A, B). Immunohistochemistry analysis was positive for CD10, CD20, and BCL2 and negative