Abstract

Pernicious anemia is an autoimmune disorder that is characterized by the presence of autoantibodies to intrinsic factor and parietal cells which results in the inability to absorb vitamin B12. It is the most common manifestation of vitamin B12 deficiency and accounts for 20-50% of cases. Disseminated intravascular coagulation (DIC) is a clinical condition that is a complication of another process which causes the activation of coagulation. A 63-year-old female with a history of hypothyroidism presented with a 1-month history of worsening fatigue, intermittent epigastric pain, nausea, vomiting, and diarrhea. Initial laboratory findings showed severe anemia and macrocytosis with a hemoglobin of 4.3 g/dL and a mean corpuscular volume (MCV) of 138 fL. There was also a significant elevation of the D-dimer, lactate dehydrogenase (LDH), and creatinine. She received three units of packed red blood cells (pRBCs) and fluid resuscitation. A vitamin B12 level was obtained which revealed a severe vitamin B12 deficiency (< 150 pg/mL). Additional workup showed seropositivity for anti-parietal cell antibodies and intrinsic factor blocking antibodies, and an esophagogastroduodenoscopy (EGD) biopsy yielded histologic findings consistent with autoimmune gastritis. She was treated acutely with daily intramuscular B12 injections with improvement in hematologic derangements and symptomatology. Arrested erythropoiesis can lead to apoptosis and the high proliferation of immature erythroblasts results in cells that are more susceptible to impaired deoxyribonucleic acid (DNA) synthesis and results in denatured DNA. Pernicious anemia manifesting as DIC has yet to be described in the literature. Here we describe an interesting case of pernicious anemia manifesting as DIC resulting from arrest of erythropoiesis evidenced by the international society on thrombosis and hemostasis score of 5, diagnostic for DIC. Early recognition and treatment of this reversible etiology of DIC is essential to the improvement of patient outcomes.

Keywords: Vitamin B12 deficiency; Cobalamin deficiency; Macrocytic anemia; Pernicious anemia; Disseminated intravascular coagulation; Pseudo-thrombotic thrombocytopenic purpura

Introduction

Vitamin B12 (cobalamin) is a well-known vitamin essential to erythropoiesis, deoxribonucleic acid (DNA) synthesis, and neurological function [1]. Deficiency of this vitamin can cause jaundice, glossitis, anemia, leukopenia, thrombocytopenia, cognitive impairment, gait abnormalities, loss of proprioception, and vibratory sense. In adults older than 60 years the prevalence is nearly 20%. Pernicious anemia is the most common manifestation of vitamin B12 deficiency, accounting for 20-50% of all etiologies. It is an autoimmune disorder that is characterized by the presence of autoantibodies to intrinsic factor and parietal cells which results in the inability to absorb vitamin B12.

Erythropoiesis is arrested in folate and vitamin B12 deficiencies. The abundance of vitamin B12 is essential to the transfer of a methyl group from 5-methyl-THF to homocysteine via methylcobalamin. The absorption of vitamin B12 is a complex process with many cofactors. Protein-bound vitamin B12 is released by stomach acid and then binds to glycoproteins. In the duodenum, vitamin B12 binds to intrinsic factor and in the terminal ileum this vitamin is absorbed [2]. When these vitamins are deficient, erythropoiesis is affected. The increased numbers of immature erythroblasts present in megaloblastic anemia results in premature death. These high proliferation rates result in progenitor cells that are more susceptible to impaired DNA synthesis [3]. In 2.5% of patients, cytoskeletal fragility may contribute to schistocyte formation causing a pseudo-thrombotic thrombocytopenic purpura (TTP) [4, 5]. When vitamin B12 deficiency is diagnosed, the cornerstone of treatment is replacement with cobalamin either intramuscularly or orally depending on the severity [1, 5].

Disseminated intravascular coagulation (DIC) is a clinical condition that is a complication of another disease resulting in activation of coagulation. Clinical conditions that are known to be associated with DIC includes severe infections, malignancy, severe trauma, obstetrical catastrophes, vascular abnormalities, and severe immunologic reactions [6]. Recent literature has suggested that neutrophil extracellular traps...
composed of denatured DNA, entangling neutrophils, platelets, fibrin, and cationic proteins may play a role in the development of thrombus depositions. The laboratory findings consistent with DIC include low platelet count, prolonged coagulation assays, and increased fibrin degradation products which includes D-dimer. It is important to highlight that isolated laboratory findings have limited efficacy in diagnosing DIC. A constellation of objective findings can suggest early DIC. An algorithm has been developed by the International Society on Thrombosis and Hemostasis (ISTH), which is calculated using platelet count, prothrombin time, fibrin related markers, and fibrinogen. In a prospective study, an ISTH DIC score of 5 or greater diagnosed DIC with a sensitivity of 93% and a specificity of 98% [7]. Here we describe a severe case of pernicious anemia that manifested with findings consistent with DIC.

Case Report

Investigations

A 63-year-old female with a history of hypertension and hypothyroidism was admitted due to symptomatic anemia. The patient endorsed a 1-month history of intermittent epigastric pain, nausea, vomiting, and diarrhea. The patient also endorsed worsening fatigue, especially on exertion. On physical exam patient was tachycardic, had pale conjunctiva, delayed capillary refill and was without focal neurological deficits.

Diagnosis

On admission, she was found to have severe macrocytic anemia, with hemoglobin (Hb) of 4.6 g/dL, mean corpuscular volume (MCV) of 141 fL, and reticulocyte count of 11.1%. The patient was also thrombocytopenic with platelet count of 122 × 10^3/µL, significantly elevated D-dimer (5,500), lactate dehydrogenase (LDH) of 2,008 U/L, and a creatinine (Cr) of 2.37 mg/dL with a baseline of 0.86 mg/dL. Patient’s platelet count was 50 × 10^3/µL at its lowest. Patient on admission was afebrile, without leukocytosis, and did not endorse other symptoms effectively ruling out sepsis. Peripheral blood smear was significant for the presence of hyper-segmented neutrophils and teardrop cells. The patient’s B12 level was severely depleted with levels < 150 pg/mL. Folate level was normal. During the hospitalization, the patient underwent esophagogastroduodenoscopy (EGD) with biopsy, which revealed histology consistent with autoimmune gastritis and seropositivity for anti-parietal cell antibodies and intrinsic factor blocking antibodies consistent with pernicious anemia.

Table 1. Summary of Serum Analysis

| Test              | Admission | Tx day 1 | Tx day 2 | Tx day 3 | Discharge | 1 week follow-up | 1 month follow-up | Reference range |
|-------------------|-----------|----------|----------|----------|-----------|------------------|-------------------|-----------------|
| Hb (g/dL)         | 4.3       | 9.7      | 9.3      | 10.1     | 10.0      | 10.7             | 10.4             | 11.5 - 16       |
| MCV (fL)          | 138       | 104      | 106      | 106      | 108       | 107              | 98.6             | 78 - 100        |
| Plt (× 10^3/µL)   | 76        | 50       | 50       | 68       | 115       | 548              | 272              | 130 - 450       |
| Reticulocyte      | 11.1%     |          |          |          |           |                  |                  |                 |
| PT (s)            | 13.2      | 12.8     | 12.2     | 13.2     | 13.7      |                  |                  |                 |
| D-dimer (ng/mL FEU) | 5,564   |          |          |          |           |                  |                  | ≤ 500           |
| Cr (mg/dL)        | 2.37      | 1.53     | 1.49     | 1.39     | 1.19      | 0.99             | 1.26             | 0.60 - 1.40     |
| LDH               | 2,008     |          |          |          |           |                  |                  |                 |
| B12 (pg/mL)       | < 150     |          |          |          |           | 1,345            | 232              | 1,245           |

A timeline of this patient’s objective lab findings was shown during her hospital course and at two subsequent follow-up appointments after the appropriate treatment was started. Tx: treatment; Hb: hemoglobin; MCV: mean corpuscular volume; Plt: platelet; LDH: lactate dehydrogenase; Cr: creatinine; PT: prothrombin time.

Comparison

Treatment

During her hospitalization, treatment with intramuscular B12 injections (1,000 µg) were initiated. The patient received three units of packed red blood cells (pRBCs) and a repeat Hb level was 9.7 g/dL. She was started on a daily regimen of B12 injections and continued for 1 week upon discharge. Patient’s treatment with subcutaneous B12 injections resolved hematological derangement and her clinical status improved.

Follow-up and outcomes

At the patient’s 1-week follow-up, labs were significant for Hb of 10.7 g/dL, MCV of 107 fL, and a platelet count of 548 × 10^3/µL with resolving symptoms of fatigue and increased activity tolerance. At the patient’s 1-month follow-up, the patient’s lab values were significant for a Hb of 10.4 g/dL, MCV of 98.6 fL, and platelet count of 272 × 10^3/µL. A vitamin B12 level obtained at that time was 1,345 pg/mL. A timeline of the patient’s lab findings can be found in Table 1. The patient was then transitioned to high-dose oral supplementation of cyanocobalamin 1,000 µg, twice daily, which will be continued indefinitely.
Discussion

There are numerous etiologies of B12 deficiency, or cobalamin deficiency, the most common being pernicious anemia. In this condition there is autoimmune destruction of parietal cells. This pathology also results in decreased intrinsic factor which carries a critical role in B12 absorption. Although these individuals may have an adequate diet, they still can become profoundly deficient in cobalamin [2]. Pathological findings of this disorder include loss of gastric mucosal folds and thinning of the gastric mucosa. In the autoimmune type, the fundus and body are affected while the antrum is spared. The nonautoimmune type involves the fundus, body, and antrum. Histologically, mononuclear cellular infiltrates are present in the submucosa extending into the lamina propria between the gastric glands [5].

There have been several rare cases of atypical manifestations of vitamin B12 deficiency. Cobalamin can affect erythropoiesis and lead to an arrest in the maturation of nucleated precursors and results in bone marrow hemolysis causing a presentation that can mask symptoms of microangiopathic hemolytic anemia [8-10]. Pernicious anemia can also cause symptoms of thrombocytopenia, schistocytosis, and elevated LDH. The literature has described cases that differentiate TTP from pseudo-TTP. Pseudo-TTP is a phenomenon where pernicious anemia can mimic symptoms of TTP [4, 11, 12]. Several authors have presented similar cases of TTP as a rare presentation of pernicious anemia.

In this case the proposed mechanism of DIC as a result of pernicious anemia can be attributed to the rapid ineffective erythropoiesis. Due to the immaturity of these erythroblasts, they are more vulnerable to cell death and apoptosis [3]. Cells that have undergone this process can then act as microthrombi. The denatured DNA that occurs due to the impaired DNA synthesis in vitamin B12 deficiency can cause intravascular webs, described as neutrophil extracellular traps. These can aid in the development of thrombi and has been described as a possible contributor to the development of DIC [6, 13].

It is essential to differentiate the clinical manifestations of pernicious anemia and DIC. In this case, microvascular manifestations of thrombosis such as an increase in creatinine from baseline, consumption of platelets and a severely low Hb can lead a practitioner to believe that these hematological arrangements could be because of DIC. DIC and pernicious anemia have key findings that overlap such as these hematological derangements of low Hb and thrombocytopenia. However, it is essential to delineate that pernicious anemia includes increased MCV, increased reticulocyte count, low vitamin B12 level, and a positive intrinsic factor. DIC is a complication of another diagnosis, typically severe infections, malignancy, severe trauma, obstetrical catastrophes, vascular abnormalities, and severe immunologic reactions [6]. In this case, erythropoietic failure is responsible for the development of early DIC.

Conclusions

Typically, vitamin B12 deficiency presents as symptomatic anemia occasionally with additional hematologic changes and neurological symptoms. There are few cases that describe derangements in erythropoiesis, mimicking other etiologies. Pseudo-TTP has been well described in the literature with symptoms of thrombocytopenia, schistocytes, and elevated LDH as a rare presentation of pernicious anemia. A case of pernicious anemia manifesting as DIC has yet to be described in the literature. In this case, the patient was found to have thrombocytopenia, severely increased fibrin-related markers such as D-dimer, which under ISTH criteria would correlate to a score of 5 which is compatible with overt DIC [14, 15]. With the administration of intramuscular vitamin B12, the patient’s symptoms resolved and the patients DIC score became zero. Understanding and early recognition of this reversible presentation of DIC can minimize patient morbidity and mortality.

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Financial Disclosure

None to declare.

Conflict of Interest

The authors report no conflict of interest.

Informed Consent

Written informed consent was obtained by the patient.

Author Contributions

MBA and LR contributed to the manuscript. AE and SWT provided direct clinical care. All authors read and approved the final manuscript.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

Abbreviations

Cr: creatinine; EGD: esophagogastroduodenoscopy; Hb: hemoglobin; ISTH: Internal Society of Thrombosis and Hemostasis; MCV: mean corpuscular volume; Pt: platelet; pRBCs: packed red blood cells; TTP: thrombotic thrombocytopenic
purpura

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