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Evans Syndrome in Rectal Carcinoma

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Abstract
Malignancy is rarely associated with autoimmune disease, and it may complicate into rare conditions such as Evans Syndrome (ES). ES is an infrequent condition that manifests as a combination of Autoimmune Hemolytic Anemia (AIHA) with Immune Thrombocytopenic Purpura (ITP). There were reported cases of ES associated with hematological malignancy but association with rectal carcinoma is relatively unknown. We report a case of a young gentleman with stage III rectosigmoid adenocarcinoma who underwent successful oncological resection and presented a month later with severe anemic symptoms. Blood investigations were consistent with AIHA and ITP. He was treated with steroids and received multiple blood transfusions but eventually succumbed to death.

Keyword
Evans Syndrome; Rectal Carcinoma, Autoimmune Hemolytic Anemia, Immune Thrombocytopenic Purpura, Thrombotic Thrombocytopenic Purpura

Introduction

AIHA (Autoimmune Hemolytic Anemia) and ITP (immune thrombocytopenic purpura) are the hallmarks of the uncommon autoimmune disease Evans Syndrome (ES) [1,12]. The presentation of ES is more complex other than other autoimmune disease and often misdiagnosed, leading to improper management. While the condition poses significant challenges in diagnosis and management, its association with rectal carcinoma may complicate the situation. To the best of our knowledge, this is the first case of rectal adenocarcinoma associated with ES in our country.

Case Presentation

36-year-old Malay gentleman who was diagnosed with stage III rectosigmoid adenocarcinoma. He successfully underwent open anterior resection and was planned for adjuvant chemotherapy. A month later, he presented with lethargy and reduced effort tolerance. Physical examination revealed the presence of pallor and jaundice while other systemic examinations were unremarkable.

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Blood investigation showed anemia with thrombocytopenia, deranged renal profile, transaminitis, and indirect hyperbilirubinemia. Full Blood Picture (FBP) showed hypochromic microcytic anemia, schistocytes, fragmented and nucleated red blood cells (RBC), polychromasia, spherocytes, and microspherocytes (Figure 1 and Figure 2). Besides that, leukocytosis, neutrophilia, lymphocytosis, and thrombocytopenia were also present. The direct antiglobulin test showed strong positivity with specific detection of Immunoglobulin G. However, Indirect Antiglobulin (IAT) for this patient was negative. Lactate dehydrogenase was markedly elevated. Urinary analysis showed strong positivity of hemolysis while other parameters are normal [Table 1]. Subsequently, this patient was diagnosed with Evans syndrome. Esophagogastroduodenoscopy (OGDS) was done to exclude upper gastrointestinal bleeding and the result was normal. Since this patient was sent to us from another facility, prior blood investigation cannot be compared.

The patient began receiving intravenous methylprednisolone that was administered at a dose of 1 gm for three days and then oral prednisolone at a dose of 1mg/kg for one week. Additionally, the patient had many transfusions of blood products, mostly packed cells. Nevertheless, despite the treatment, the hemoglobin level remained low. He succumbed to death less than a month later due to severe anemia secondary to ES.

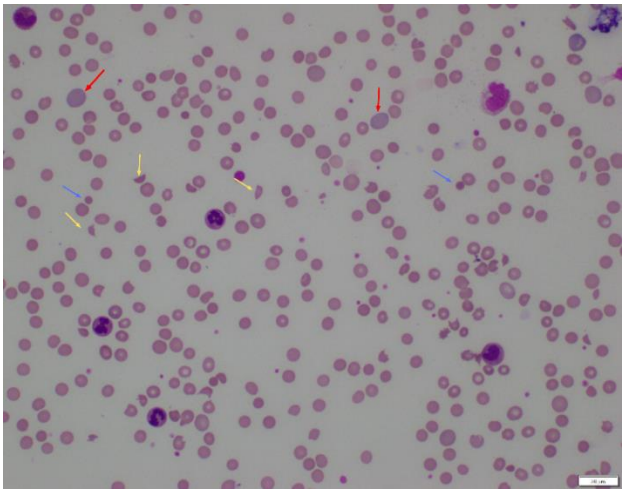

Figure 1: Full Blood Picture of the patient, magnification at 20x: Red Arrow – polychromasia, Yellow Arrow – schistocytes, Blue Arrow – microspherocytes

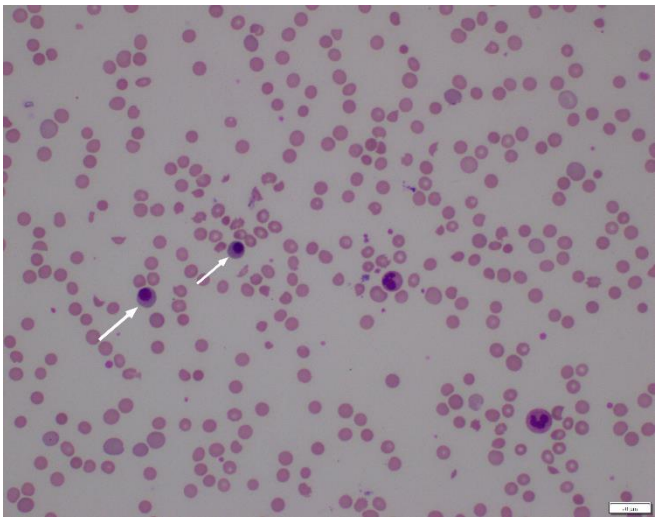

Figure 2: Full Blood Picture of the patient, magnification at 20x: White Arrow – Nucleated RBC

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Table 1 Blood investigations upon admission to our centre.

Blood	Abbreviation	Result	Normal Value
Red Blood Cell			
White Blood Cell	WBC	36.2	4.0-10.0 10x9/L
Hemoglobin	HB	5.4	13.0-17.0 10x9/L
Platelet	PLT	157	150-410 10x9/L
Reticulocyte count	RETIC	7.6%	0.2-2.0%
Renal Function Test			
Urea		23.0	2.8-7.2 mmol/L
Creatinine		186	59-104 umol/L
Liver Function Test			
Alanine transferase		62	<45 U/L
Aspartate transaminase		69	<75 U/L
Alkaline phosphatase		849	80-120 U/L
Total Bilirubin	TB	39.4	5.0-21.0 umol/L
Direct bilirubin		10.5	<3.4 umol/L
Other Serology Blood Test			
Direct Antiglobulin Test	DAT	Positive (+)	
Lactate dehydrogenase	LDH	2690	<248U/L
C – Reactive Protein	CRP	130.7	<5mg/L
Urine analysis • Blood • Bilirubin • Urobilinogen • Leucocyte		 Positive Negative Negative Negative	

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Discussion

ES is a rare medical condition. It is characterized by the occurrence of two autoimmune diseases which are AIHA and ITP simultaneously. It was first identified and described by Evans in 1951 [1]. The incidence of ES is exactly unknown. But there was a retrospective study conducted in Denmark with data collected from the year 1980 to 2016 and concluded that ES has commonly affected females aged 50 to 60 years old. ES can also be presented as a secondary disease and mostly as complication of hematological malignancies. The mortality of ES is high, especially within the first year of diagnosis [2]. This is clearly observed in our case whereby our patient died a month after the diagnosis of ES was made.

The exact cause of ES is still unknown thus it is often considered as an idiopathic condition. Most of the published studies involved a small number of patients, and the recommended approach to ES is not well established. ES may also be associated with autoimmune cytoproliferative syndrome and other hematological malignancies such as Chronic Lymphocytic Leukemia, Hodgkin's Lymphoma, and Multiple Myeloma [3].

The patient of ES may present with signs and symptoms of ITP or AIHA or a combination of both. The presentation of AIHA includes pallor, fever, jaundice, hemoglobinuria, and splenomegaly. On the other hand, symptoms of patient with ITP are the symptoms are due to purpura, followed by bleeding tendencies such as gingival bleeding, epistaxis, hematuria, melena, and even worse intracerebral hemorrhage [4].

In general, panels of blood investigations are carried out based on the patient's presentation itself. The diagnosis of AIHA is confirmed by the presence of reticulocytosis, elevated lactate dehydrogenase (LDH) levels, decreased haptoglobin, elevated indirect bilirubin, positive serum-free hemoglobin, and positive urine hemosiderin. In addition, a positive Direct Antiglobulin Test (DAT) may help with the diagnosis, but DAT may appear positive in healthy adults [5]. The Red Blood Cell (RBC) of the ITP showed isolated thrombocytopenia with a count of less than 100 x109/L while the other parameters are normal [6]. Thus, the confirmation of ES is a combination of the laboratory findings of AIHA and ITP.

FBP is the routine investigation to ascertain evidence of hemolysis. Polychromasia, which indicates reticulocytosis, may be observed in FBP results. Spherocytes, which are abnormally shaped red blood cells, are often seen in patients with moderate to severe hemolytic anemia. In more severe cases, FBP may also reveal the presence of RBC fragments, nucleated RBCs, and occasionally erythrophagocytosis (the ingestion of red blood cells by monocytes) [7]. Apparently, some of these findings are shown in our patient's FBP. The findings are polychromasia, schistocytes, microspherocytes (Figure 1), and nucleated RBC (Figure 2).

There is no known literature that discussed the association between rectal malignancy with ES. However, there is a case reported in the United States that ES is likely caused by the chemotherapy used to treat rectal carcinoma. The patient was a 76-year-old lady with metastatic colon adenocarcinoma who was started on a combination of chemotherapy consisting of oxaplatin, capecitabine, and bevacizumab. During a course of chemotherapy, she developed anemic symptoms. Her blood panel shows in favor of AIHA and ITP. This patient received multiple blood products and oral prednisolone. She responded well to treatment [8]. To our knowledge, this is the first case of ES in rectal carcinoma that has been reported in our country.

The treatment for ES has not been established as it lacked evidence-based studies. The primary treatment should address the underlying cause. For this patient, it is definitely surgical resection followed by adjuvant chemotherapy. But the mainstay of treatment for ES is the administration of corticosteroids with or without the use of Intravenous Immunoglobulin (IVIG) and blood product support as necessary [4]. The use of Cyclosporin or rituximab is recommended in moderate and severe cases as a second-line therapy. Splenectomy commonly achieves short-term responses. It also may reduce the frequency of relapses and

allow the reduction of immunosuppressive agents. Finally, high-dose therapy plus stem cell support may provide a cure in long term but still in clinical trials [3].

Another disease that may mimic ES is Thrombocytopenic Purpura (TTP). TTP is an autoimmune disease that happens when there is a severe lack of ADAMSTS13. ADAMSTS13 is an enzyme that processes a large protein called Von Willebrand factor (VWF). VWF is a protein that involves in coagulation cascade. These conditions will lead to microangiopathic anemia, thrombocytopenia, and ischemic end organ events. The deficiency could cause instability of the coagulation cascade, specifically VWF and factor VIII, resulting in the formation of platelet-rich thrombi in the microvasculature, thus resulting in end organ damage affecting the brain, heart, and kidneys [10]. The neurologic manifestations are common in TTP patients, which can be clinically differentiated from ES patients. The symptoms may vary from mild confusion or altered sensorium to stroke, seizures, or coma [11]. TTP is a clinical emergency, and treatment should be initiated promptly, as delays in therapy may result in significant morbidity and mortality. Severe ADAMTS13 deficiency is required to confirm the diagnosis of TTP, but it should not delay the initiation of treatment. However, the treatment is quite similar to ES and meets the main principle of the treatment, which is immunosuppression, blood support, and monoclonal antibodies if needed [11,12].

The challenges that may affect the management of ES's patient are the time and clinicians needed to make a correct diagnosis. As the time consumed to do specific blood tests and thorough specimen assessments increases, it will affect the time to manage the patient as the patient deteriorates over time as hemolysis goes on. As mentioned above, ES is the diagnosis by exclusion, and it takes a skilled clinician to make such diagnoses. With the limited data available that is discussed relatively about the ES, the clinician might not be experienced enough to manage such diagnoses, thus delaying the proper treatment.

Conclusion

In conclusion, ES associated with rectal cancer is a rare occurrence. In order to identify the disease, comprehensive laboratory tests are required, and the diagnosis itself is predicated on ruling out alternative differentials. Blood products, immunosuppressive medications, and underlying cause treatment are the cornerstones of the therapeutic regimen. A situation like this could present a problem for a doctor or surgeon because ES diagnosis is difficult enough on its own, let alone when combined with cancer, which could change how the cancer is treated. We anticipate doing a large number of clinical trials in the future to provide appropriate guidelines for the management of ES.

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