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Multiple Immune Dysregulation Conditions with a Single Underlying Root Cause of NRAS Gene-Positivity: A Case Report

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Abstract: Hematological malignancies in particular are recognized to be linked to immunological dysregulated disorders such hematolytic anemia, immunodeficiency, and autoimmune illnesses. We describe a rare case that had multiple immune dysregulation symptoms and was subsequently found to be positive for the NRAS gene. A male, 29, complained of pleuritic chest pain. On the ECG, he showed broad PR depression and elevated PR in aVR, along with elevated troponin. He received colchicine and NSAIDs as treatment with a good response and resolution of his symptoms. After four weeks, he developed a fever which thought to be secondary to perianal abscess, and a surgical incision and drainage along with broad spectrum antibiotics was used to treat a perianal abscess. Despite receiving extensive medical and surgical care, his fever persisted. His blood film started to show circulating blast cells. Following an immediate bone marrow aspiration and biopsy, there were no notable abnormalities seen, and a 1% blast was present, which was assumed to be the result of stress or infection. Later, a weak positive +1 Coombs (DAT) test is developed and caused active hemolytic anemia required blood transfusion. Along with the anemia, a wrist expanding wound was discovered in the previous IV cannula site. Clinically wound appears as a pyoderma gangrenosum. Histopathology showed purulent dermal inflammation including many neutrophils and macrophages. This feature of micro abscess formation was consisting with the diagnosis of pyoderma gangrenosum. An intravenous steroid (1 mg/kg) was administered in response to a positive Coombs test and pyoderma gangrenosum. The patient's condition greatly improved overall. His wound began to heal as his white blood cell count dropped. After being given oral steroids with a titration-down plan, the patient was sent home. A whole genome sequence was performed on him because he had peri myocarditis, pyoderma gangrenosum, and hematolytic anemia. The results show that he is NRAS gene positive. He was attentively observed clinically with regular out-patient follow-ups as this gene is strongly associated with hematological cancers. He developed symptomatic normocytic anemia a few months later, and a bone marrow aspiration and biopsy were performed to confirm the presence of Myelodysplastic syndromes (MDS). He was transferred to another facility and underwent chemotherapy and bone marrow transplant. In otherwise healthy individuals, the idea of offering a single explanation—Occam's razor—must be considered and investigated. Finding the underlying reason could improve patient care, enable precision therapy, and alter the course of events.

Keywords: Multiple Immune Dysregulations, Root Cause, NRAS Gene, Case Report.

Case Report

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INTRODUCTION

Immune dysregulation is as vital as vulnerability of patients to infections in determining primary immunodeficiencies [1]. The comprehensive understanding of immune dysregulation in several ailments continues to grow [2-4]. For instance, malignancies, especially hematological ones, are known to be associated with immune dysregulation conditions, such as immunodeficiency, hematolytic anemia, and autoimmune diseases [5]. Very often, such conditions are attributed to one single underlying root cause. However, due to variability and non-specificity of the symptoms associated with multiple immune dysregulation conditions, diagnosis may be delayed with subsequent delayed treatment of the patient [6]. This eventually may

lead to several complications, if misdiagnosed and left untreated. Such a dilemma may even become more important for younger patients with no known comorbidities.

Generally, the immune system is under regulation of multiple checkpoints and immune dysregulation may lead to abnormal functioning of immune cells, resulting in hyperinflammation, autoimmune conditions, and even malignant proliferation [7]. It is very likely that patterns of immune dysregulation may be linked to the underlying genetic abnormalities [8]. Very often, such genetic defects may be one simple possible explanation and root cause of several types of immune dysregulations [9, 10]. Identifying a simple solution by discovering the root cause may have a positive and quick influence on outcomes of the patients, especially young and otherwise healthy individuals.

The practice of identifying more proximal causes rather than one root cause is unfortunately not uncommon in the field of medicine [11]. However, such practice may divert clinicians from treating one single root etiology of several outcomes. As a result, patients may not be treated thoroughly and may present to clinic with frequent visits. In contrast, following the principle of simple rather than complex explanations may help clinicians to practice precision medicine with a focused and better patient care. Through this case report, we present a unique example of a young adult who had several immune dysregulation conditions, yet with a single underlying root cause of a single genetic defect. This case report provides useful insights into how clinicians can employ the principle of using a single and simple solution strategy to address several underlying problems for improved patient care.

Patient Information

A 29-year-old man presented to the emergency department with pleuritic chest pain. Initially, at the time of presentation, the patient was presented with chest pain and was found to have pericarditis. After four weeks, he was presented with fever and perinatal abscess, followed by blast cells in his CBC and hemolytic anemia and pyoderma gangrenosum. However, the patient was not found to have any relevant past medical or surgical history and his family history was also not significant. There was no history of blood transfusion.

Clinical Findings

At the time of presentation, he was found to be anemic, and his pain was severe in intensity. However, he developed a sequalae of symptoms after being admitted to the hospital (see below).

Diagnostic Assessment

Upon further assessment at the time of presentation, his troponin levels were found to be high. His electrocardiogram shows diffuse PR depression with PR elevation in aVR. The combination of his symptoms, clinical findings, and diagnostic assessment were suggestive of typical peri myocarditis and he was treated accordingly.

Therapeutic Interventions and Timeline

The patient was treated with NSAIDs and Colchicine. After four weeks, he started to have a fever. Upon examination, a perianal abscess was found, which was treated surgically with incision and drainage followed by broad spectrum antibiotics. However, his fever persisted despite surgical intervention, broad-spectrum antibiotic coverage, and the absence of drainable collection in the pelvic image. His complete cell counts showed low hemoglobin levels and leukocytosis, while his peripheral blood smear revealed 1-3% blasts with mild toxic changes in some neutrophils. An urgent bone marrow aspiration and biopsy were done, which showed no significant abnormality, reactive, and the presence of 1% blast thought to be due to stress/infection. Later, his anemia works up weak positive +1 coombs (DAT) test.

Follow-Up and Outcomes

A wrist wound appears in the previous intravenous (IV) cannula site along with the anemia. It became clear that this was turning out to be pyoderma gangrenosum, which was later confirmed by histopathology. Given a positive Coombs test and pyoderma gangrenosum, an intravenous steroid (1 mg/kg) was given. The patient's overall condition improved significantly. His white blood cells (WBCs) started to trend down, his hemoglobin got stabilized, and his wound started to regret and heal. The patient was discharged home on oral steroids with a titration-down strategy.

Genome Sequencing and Further Outcomes

Since the patient had multiple immune dysregulation conditions including peri myocarditis, pyoderma gangrenosum and hematolytic anemia, we performed his whole genome sequence. His genome study reveals NRAS gene positive. Since the positive NRAS gene is heavily linked to hematological malignancies, the patient was followed closely. A few months later, he was presented with symptomatic normocytic anemia. We performed bone marrow aspiration and biopsy to confirm the presence of myelodysplastic syndrome with excess blast-2 (MDS-EB-2). He was transferred to another facility and underwent chemotherapy and bone marrow transplant.

DISCUSSION

We presented a unique case of a younger patient who was presented with multiple immune dysregulations with a single underlying root cause of NRAS gene positive. The scientific evidence suggests that varying RAS genes are mutated in distinct malignancies [12, 13]. Hematological malignancies are mostly unusual where

both NRAS and KRAS, responsible for encoding a GAP (GTPase activating protein) called neurofibromin, are mutated with varying frequencies [14]. However, NRAS than KRAS mutations are predominant in hematological malignancies [12]. In addition, the studies demonstrated that somatic mutations of NRAS are found in about 20 to 40% of the myelodysplastic syndrome (MDs), heterogenous clustering of hematopoietic disorders featured by abnormal hematopoiesis, cytopenia, and higher risk of acute myeloid leukemia [15, 16]. For example, recent evidence suggests that NRAS is mutated in about 5% of MDs with adverse clinical features [17, 18]. However, these mutations are often not uniformly distributed even among individual patients. These patients have abnormal cells in their bone marrow, which evolve over time with subsequent sub-clonal groups. Somatic mutations in NRAS genes are responsible for clinical presentation and overall survival and prognosis among patients with MDs [19, 20].

Strengths and Limitations

This case provides a unique report of a patient who was diagnosed with myelodysplastic syndrome with multiple immune dysregulation conditions. This unique report guides clinicians to think of a single underlying cause of multiple conditions and such multiple conditions can be treated by targeting one root cause. This will not only save the time of clinician and patient, but will also ensure better patient care and will help to embrace the idea of precision medicine. However, the findings of this case report need to be interpreted in the light of some limitations. First, the patient was transferred to another hospital, which prevented us from making firm conclusions about the prognosis and long-term outcomes of the patient. It is unclear what type of treatment did patient received at another hospital and how did he respond to chemotherapy and bone marrow transplantation. In future, we recommend comprehensively following such patients with short- and long-term outcomes.

CONCLUSION

The main take away from this case report is to follow the principle of Occam's razor, which implies that a single and simple explanation can be possible for multiple complex outcomes. Such single cause of multiple outcomes needs to be addressed, especially among healthy individuals. Discovering the root cause may change outcomes and may help to focus on precision medicine and better patient care.

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