CLINICAL VIGNETTE

Pneumocystis Jiroveci Pneumonia in a Patient with Occult Myelodysplastic Syndrome

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An 82-year-old male presented to the Emergency Department (ED) with progressive generalized weakness and cough for two months. He reported one week of worsening cough, exertional dyspnea and intermittent chills, which prompted his family to bring him to the ED. He denied weight loss, night sweats, chest pain, hemoptysis, nausea, vomiting or any change in his bowel habits. Past medical history was significant for type 2 Diabetes, hypertension and Gastroesophageal reflux disease (GERD). He denied any significant family history, specifically no cancer or bone marrow disorders. He lived with his daughter in California but travelled to Mexico on a regular basis. He was a former forty-pack year smoker but quit 20 years ago.

In the ED, he was febrile, in mild respiratory distress, with T 39.2 C, BP 114/85 mmHg, HR 110/min and RR of 28. His SPO2 was 96% on 2L NC. His general physical examination was essentially normal, including cardiovascular, respiratory and abdominal exams. He had intact pulses, no peripheral edema and was alert and oriented with no focal neuro deficits.

His laboratory testing showed pancytopenia with WBC count of 19.0 x10E3/μL, absolute neutrophil count of 600, hemoglobin of 7.4 g/dl, MCV of 109.7 and platelet count of 101 x10E3/μL. Lactic acid was mildly elevated at 2.1. Chemistries included normal liver enzymes and electrolytes with elevated BUN of 35 and Cr of 2.35 mg/dl. Urinalysis showed only mild proteinuria, and Chest X-Ray was remarkable for bibasilar lung opacities and mild cardiomegaly.

He was admitted with sepsis of pulmonary origin and in light of fever and neutropenia, intravenous Cefepime was initiated. Blood cultures, urinary legionella antigen, urinary streptococcal antigen and PCR respiratory panel were all negative.

Intermittent fevers persisted despite intravenous Cefepime prompting additional evaluation. CT Chest without contrast revealed bilateral pulmonary infiltrates with tree-in-bud opacifications, nodular densities in the right middle lobe as well as large mediastinal lymph nodes with the largest measuring 4.9x4.6 cm in size. Histoplasmosis urine and serum antigens, Cryptococcal serum antigen, Galactomannan and 1,3 D-Glucan all returned negative. Coccidioidomycosis immunodiffusion (ID) and Complement Fixation (CF) samples were sent to the reference laboratory, which resulted in positive ID IgM and negative CF. Quantiferon was also borderline positive.

Infectious disease and pulmonary services were consulted and in view of his persistent neutropenia, bronchoscopy and bronchoalveolar lavage was recommended to better visualize the respiratory system and obtain appropriate samples. Intravenous Fluconazole was started considering his positive immunodiffusion test for coccidioidomycosis and imaging findings on Chest CT. His large mediastinal lymph nodes were deemed to be reactive secondary to infection and close follow up was recommended.

Bronchoalveolar lavage with brushing samples resulted in positive Pneumocystis Jiroveci (formerly known as PCP) PCR, however, PJP cytology was negative. Mycobacterium TB PCR and smear, bacterial culture and fungal culture all returned negative. BAL Cytology did not show any evidence of malignancy.

Considering the positive PJP PCR in the setting of pulmonary infection in an immunocompromised host, intravenous trimethoprim-sulfamethoxazole was added to his antimicrobial regimen to target PCP. His PaO2 was 72 and concomitant use of corticosteroid was not recommended. Patient's quantiferon was positive but Mycobacterium tuberculosis and resistance to rifampin assay (MTB IRF) was negative. As the patient had negative smears and PCR test for TB the decision was made to continue close monitoring without TB drugs.

The patient's pancytopenia persisted and Hematology-Oncology was consulted. After careful review of his past record, they found early signs of pancytopenia one year prior to his hospitalization with an insidious course. Considering progressive macrocytosis, differential diagnoses included maturational disorder versus bone marrow infiltrative disorders and as there was no evidence of nutritional deficiency and bone marrow biopsy was recommended. Bone marrow biopsy reported hypercellular (80% cellularity) with 14% blasts within marrow which was consistent with Myelodysplastic Syndrome (MDS).

His hospital course was further complicated by acute kidney injury with creatinine increasing from 1.7 to 2.44 mg/dl three days after initiation of Trimethoprim-Sulfamethoxazole. Acute kidney injury (AKI) evaluation was unrevealing and was attributed to Trimethoprim-Sulfamethoxazole. This was discontinued and replaced with Atovaquone.

The patient continued to have intermittent high grade fevers with attempts to de-escalate antibiotic therapy which led to a

prolonged hospitalization. However, after multiple blood cultures remained negative, broad spectrum antibiotics were discontinued after completion of a course for neutropenic fever. A 21-day course of Atovaquone was completed and after >48 hours of being afebrile he was discharged to a skilled nursing facility with plan to follow up closely as an outpatient to discuss management of coccidioidomycosis, mediastinal lymphadenopathy and MDS. His antimicrobial therapy on discharge included Fluconazole and daily Levofloxacin as a prophylactic measure in setting of neutropenia.

Discussion

Myelodysplastic syndromes (MDS) are clonal disorders of hematopoietic stem cells in which immature blood cells in the bone marrow do not mature to become healthy blood cells. This leads to blood cytopenias as well as a high risk of progression to acute myeloid leukemia (AML). MDS is classified into low, intermediate and high risk, which allow prognostication by an international prognostic scoring system (IPSS). Treatment for low risk MDS is typically aimed at correcting cytopenias, whereas higher risk patients may receive treatments including azacitidine or decitabine aimed at modifying the disease process. Infection is a well-known complication mainly due to a decrease in quantity and quality of neutrophils. Despite the long course, there is limited information on bacterial, fungal and viral infections. However, one retrospective trial of 238 untreated low to intermediate risk MDS patients who died between 1980 to 2004, found infection was the most common cause of death (38%), followed by AML transformation (15%).[1]

Given the significant morbidity and mortality of infection related to MDS, it is important to recognize the infectious risks in both treated and untreated patients with MDS. Patients presenting with significant pancytopenia and unknown diagnosis should undergo bone marrow aspirate and biopsy to help establish a diagnosis.[2] This patient presented with both pancytopenia and pulmonary symptoms and fevers. CT scan showed bilateral pulmonary infiltrates with tree in bud opacities followed by bronchoscopy and BAL. The literature cites usefulness of bronchoscopy in early identification of pathogens with significant impact on survival.[3] Bronchoscopy was most effective at identifying pneumocystis and herpes virus pneumonia, with less sensitivity and specificity for fungal and bacterial pneumonias.[3] When a causative agent is discovered on bronchoscopy including BAL, therapy can be tailored and targeted with an overall improvement in care.

Pneumocystis jiroveci (PJP) is an opportunistic infection most associated with HIV/AIDS in the setting of neutropenia and low CD4 cells. However, it is also found in patients with hematologic malignancy. One study of patients with hematologic malignancies, identified PJP, via brochoalveolar lavage in a majority of cases followed by treatment with trimethoprim-sulfamethoxazole, Pentamidine, Dapsone or Atovaquone.[4] Our patient was initially treated with trimethoprim-sulfamethoxazole, but developed AKI and was switched to Atovaquone with stabilization and improvement in kidney function.[5]

Diagnostically, the patient had negative microscopy but a positive qPCR for PJP. He was started on PJP treatment based on qPCR results with clinical improvement with treatment. A four-year prospective trial compared diagnostic criteria in immunocompromised patients for PJP, and found threefold more patients identified with positive qPCR than direct examination of microscopy. Those with positive qPCR testing but negative microscopy were subsequently placed into 3 categories: retained (PJP retained as the final diagnosis), possible (PJP was considered possible but not formally retained), and the rest were considered colonization. The diagnosis was considered retained when (i) when at least 3 of the 4 following items were present, cough, fever, dyspnea, compatible radiographic findings, and (ii) a favorable outcome was obtained after therapy, without other infectious agents or (iii) PCP was confirmed post-mortem.[6] Our patient fit these criteria with fever, cough, dyspnea and radiographic findings, along with an improved outcome after therapy. The study also found that qPCR was a useful tool in diagnosing PJP particularly in non-HIV patients. Patients without HIV accounted for 53% of PJP diagnosis by microscopy and 69% of cases when pooled with the isolated qPCR positives.[6] Patients with hematologic malignancies (13 out of 17) were mostly likely to have an isolated qPCR positive test and a retained diagnosis of PJP.

In patients with pancytopenia, particularly neutropenia, infection is a common cause of morbidity and mortality. While bacterial and viral pneumonias are most likely, it is important to remember opportunistic infections, in particular PJP. A recent study reported PJP remains a severe disease associated with high rates of mechanical ventilation and mortality. The 90-day mortality was 27%, increasing to 50% in the severe PJP group.[7] Given how often PJP can present in hematologic malignancy and the severity of disease, it is important to utilize all diagnostic modalities. In those with hematologic malignancies and negative microscopy, qPCR offers addition opportunity for PJP diagnosis which may allow for early tailored and effective treatment.

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