Atypical Parenchymal Pulmonary Presentation of Steroid-Resistant Familial Mediterranean Fever Treated with Colchicine

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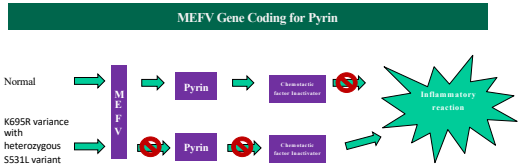
Abstract

Familial Mediterranean Fever (FMF) is an autosomal recessive autoinflammatory disorder involving mutations of the MEFV gene which encodes for pyrin(1). Typical symptoms of FMF include acute intermittent episodes of fevers lasting one to three days associated with polyserositis, which are relieved with oral colchicine. This case report describes a patient with an atypical parenchymal pulmonary presentation of FMF successfully treated with colchicine.

Case Description

A 60-year-old male of Italian and Polish ancestry presented with a one-year history of chronic dyspnea on exertion associated with a productive cough and intermittent diaphoresis. On initial presentation, he was hypoxic into the low 80s on room air and tachycardic to the 110s. A chest computed tomography scan demonstrated diffuse ground glass haziness of the majority of the pulmonary parenchyma with centrilobular nodules and scattered areas of peripheral nodules with mediastinal and hilar lymphadenopathy. The pulmonary function testing demonstrated a mild reduction of diffusing lung carbon monoxide (DLCO). The bronchoscopy with bronchoalveolar lavage and biopsies showed diffuse erythema of airways with 85% lymphocytes, a CD4/CD8 ratio of 5.5 with no atypical flow cytometry. The bronchoscopy culture had rare Citrobacter freundii and Escherichia coli. There was no growth for acid-fast bacilli, fungi or pneumocystis organisms. Biopsy revealed fragments of pulmonary parenchyma and respiratory mucosa with poorly formed non-necrotizing granulomas, not consistent with malignancy. Multiple therapies were trialed including courses of azithromycin, doxycycline, trimethoprim/sulfamethoxazole and moxifloxacin, oral prednisone tapers, azathioprine, fluticasone propionate/salmeterol and leflunomide with minimal improvement. The patient continued to develop progressive hypoxia with oxygen saturation as low as 69% requiring 6 liters of home oxygen and 40 mg of daily prednisone. Whole exome sequencing was performed which revealed a heterozygous genetic mutation of the MEFV gene with p. K695R variance as well as a heterozygous S531L variant. Started on 0.6 mg of oral colchicine three times daily, and within two months, the patient was weaned from daily oral steroids and oxygen supplementation.



Clinical Images

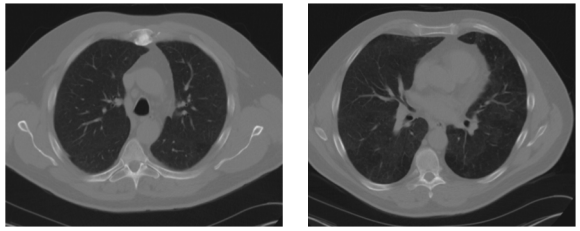


Figure 1: Diffuse ground-glass haziness with Centrilobular nodules and hilar lymphadenopathy

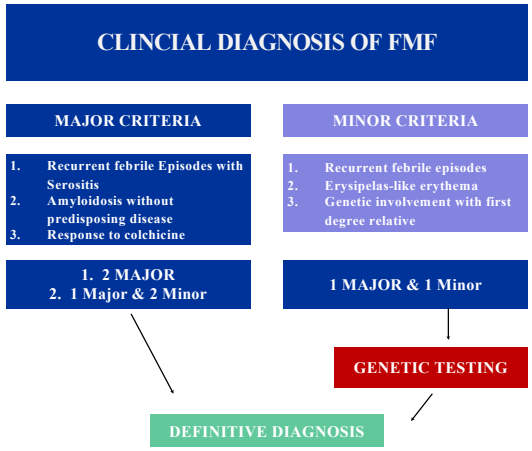


Figure 2: Tel Hashomer Criteria for Clinical Diagnosis of FMF

Discussion

FMF is an autoinflammatory disease characterized by periodic episodes of fevers and recurrent serositis with an increase in acute phase reactants (1). Most sporadic cases recorded are among the Ashkenazi Jews, Germans, and Anglo-Saxons and have been reported with rare incidences involving Asian descendants (2,6). Atypical pulmonary presentation of FMF is rare, and a few cases with pulmonary embolism, granulomas, pleuritis, infectious pulmonary paragonimiasis and complicated bilateral pneumonia (3,4,5,7,8) have been recorded. But, to our knowledge, none have shown centrilobular nodules and hilar lymphadenopathy on imaging.

Because of the rarity of isolated pulmonary involvement in FMF, it created a broad and challenging differential for our patient. Standard treatments of antibiotics and steroids did not show the response for basic pathologies such as emphysematous disease, bronchitis or bacterial or viral pneumonia. A CT with diffuse ground-glass haziness with centrilobular nodules and hilar lymphadenopathy expanded the differential to include possibly ILD, lymphocytic interstitial pneumonitis or Langerhans histiocytosis, although no cystic lesions, honeycombing, bronchiectasis, or centrilobular granulomas were seen on imaging which making these less likely. Bronchoscopy with BAL decreased the likelihood of infectious causes with negative fungal, TB and PCP cultures. Eighty-five percent lymphocytes with no macrophages present on histology and being steroid refractory made eosinophilic pneumonia unlikely. Biopsy ruled out malignancies, and an autoimmune evaluation was negative. The patient continued to decline despite a thorough evaluation of vast possible diagnoses.

Based on the Tal Hashomer criteria (fig 2) with a positive response to colchicine and recurrent diaphoresis, genotyping was pursued for the patient, showing heterozygous genetic mutation of the MEFV gene (1,9). Although FMF is usually inherited in an autosomal recessive manner, some individuals with detectable heterozygous variants can develop symptoms, as seen in our patient.

Conclusions

This case report demonstrates an adult with atypical symptoms of FMF with a heterozygous variant with pulmonary parenchyma involvement resistant to standard therapy and complete response resolution of symptoms with colchicine. It illustrates the importance of a broad differential and the potential importance of genetic testing for unusual diseases with pulmonary involvement. Clinicians should consider genetic evaluation for patients with undetermined pulmonary manifestations refractory to standard treatment.

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