Cases from the Clinic
Maryland ACP Meeting
January 30, 2016

Bimal Ashar, MD, FACP

D. William Schlott, MD Associate Professor of Medicine

Johns Hopkins University School of Medicine

CASE 1: GK

- 46-year-old gentleman who presents to establish care
- Complained of a 5-year history (started at age 41) of intermittent abdominal pain and bloating:
  - Diffuse around the epigastrium
  - Associated with fevers, chills, and nausea at times
  - Not typically related to eating
  - Experiences diarrhea and constipation at times (not consistent)
  - No distinct periodicity to the “attacks”

GK History

- PMH: Intermittent low back pain, Right inguinal hernia
- PSH: Lasik surgery, tonsillectomy
- MEDS: None
- SH: Never smoked, drinks 1-2 drinks per week, no history of drug use
- Employment: Environmental engineer—works in an office. No known occupational exposures
- FH: Mother was a diabetic who died at 84 of stroke; Father died at 70 of CHF

GK—Chart review

- Comprehensive metabolic panel—normal
- Amylase and lipase—normal
- Complete blood count—normal
- CT scan and ultrasound of abdomen revealed gallstones with no evidence of ductal dilatation or gallbladder wall thickening

GK Continued

- Underwent cholecystectomy but pain recurred
- Subsequently had colonoscopy, upper endoscopy, and upper GI series that were all unremarkable
- Ultimately treated with anti-spasmodics for irritable bowel but did not seem to help
- What now??

Differential Diagnosis

- Irritable bowel
- Inflammatory bowel disease
- Pancreatitis
- Renal colic
- Intermittent intestinal obstruction (intussusception, hernia)
- Peptic ulcer disease
- Abdominal migraine
- Mesenteric ischemia
- Behcet's disease
- Diverticulitis
- Acute intermittent porphyria
- Hereditary periodic fever syndrome (e.g., Familial Mediterranean fever)

GK—During an attack

- HPI:
  - Left-sided abdominal pain for about 24 hours. No nausea, vomiting, diarrhea, constipation, melena, or hematochezia
- Physical exam
  - VS: T– 37.4˚ C (99.4˚ F), P– 100, BP—140/80
  - GA: No acute distress
  - Abdomen: Soft, non-distended, left-sided to epigastric tenderness. No rebound/guarding

GK--Labs

	Initial Visit	During Attack
ESR (mm/hr)	15	20
WBC (per $mm^{3)}$	5.9K	12.2K
Urine red cells/white cells	None	None
LFT's	Normal	Normal
Amylase/lipase	--	Normal
Abdominal CT	--	Unremarkable

Differential Diagnosis

- Irritable bowel
- Inflammatory bowel disease
- Pancreatitis
- Renal colic
- Intermittent intestinal obstruction (intussusception, hernia)
- Peptic ulcer disease
- Abdominal migraine
- Mesenteric ischemia
- Behcet’s disease
- Diverticulitis
- Acute intermittent porphyria
- Hereditary periodic fever syndrome (e.g., Familial Mediterranean fever)

GK--Labs

- 24-hour urine for porphobilinogen and δ-aminolevulinic acid was normal

- Presumptive diagnosis: Familial Mediterranean Fever (FMF)

FMF Overview

- Autosomal recessive genetic disorder
- Primarily affects populations surrounding the Mediterranean basin
- Characterized by recurrent attacks of fever, peritonitis, pleuritis, arthritis, or erysipelas-like skin disease

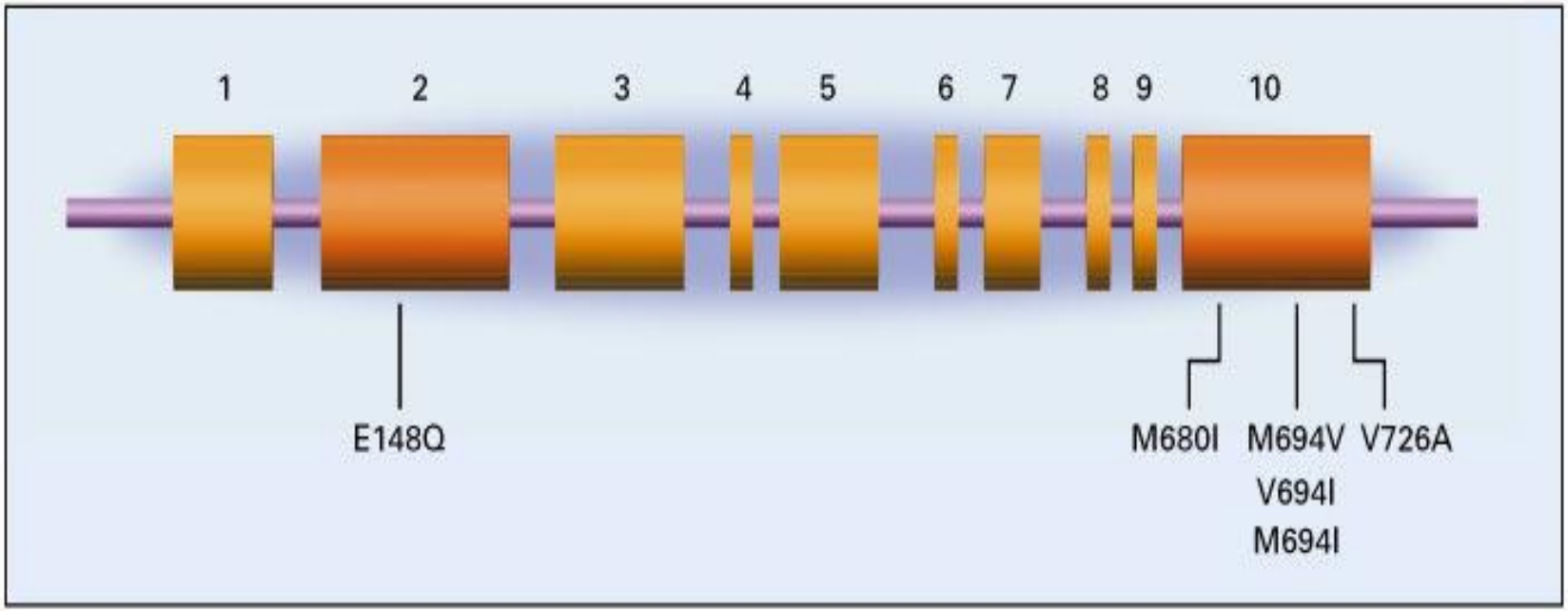
FMF—Historical Perspective

- 1st case probably described by Theodore Janeway in 1908
- Described as a distinct disease "Benign Paroxysmal Peritonitis" in 1945
- FMF gene (MEFV) cloned in 1997

MEFV Gene

- Maps to the short arm of chromosome 16
- Predominantly expressed in neutrophils
- More than 50 mutations have been identified
- Most reported cases result from 5 mutations
- Encodes a protein called pyrin (marenostrin) that is thought to repress a pro-inflammatory molecule and/or up-regulate an anti-inflammatory protein

Structure of the Gene for Familial Mediterranean Fever (MEFV)



Drenth, J. P. H. et al. N Engl J Med 2001;345:1748-1757

Epidemiology

- Primarily affects Armenian, Arab, North African, Turkish, and Jewish populations
- Prevalence may be as high as 1:200 in certain populations
- Cases now seen throughout the world

Clinical Presentation

- 90% of patients present before age 20
- Attacks usually last 1-3 days and recur within weeks to months
- Severity of attacks can vary
- Labs: Increased acute phase reactants

Fever (38.5°-40° C)	96%
Peritonitis	91%
Pleuritis	57%
Arthritis/Arthralgias	45%
Erysipeloid erythema	13%
Pericarditis, orchitis, splenomegaly, meningitis, myalgia	rare

Diagnosis

- Usually based upon clinical presentation
- Tel Hashomer criteria: (Livneh, et al. Arthritis Rheum 1997;40:1879-85)
  - Major criteria: recurrent febrile episodes with serositis, amyloidosis type AA without predisoposing disease, favorable response to colchicine
  - Minor criteria: Recurrent febrile episodes, erysipelas-like erythema, FMF in a 1st degree relative
  - Definitive Dx: 2 major or 1 major and 2 minor
- Role of genetic testing?

Treatment

- Colchicine is the mainstay of therapy based on observations in the 1970's
- Observational studies show that it can decrease the number and intensity of attacks and prevent the development of amyloidosis
- Mechanism is unclear but probably acts in a number of ways to inhibit the inflammatory response and prevent assembly of amyloid fibrils
- Dose in adults is 1-2 mg/day

Back to GK

- Started on a trial of colchicine at 0.6 mg BID
- Genetic test obtained revealing that he is homozygous for the V726A mutation
- Has not had an attack in 15 years

Learning Points

1. FMF can be seen in patients of virtually all ethnic backgrounds
2. Attacks do not need to be severe
3. Genetic testing can play a role in diagnosis
4. Colchicine is very effective for prevention of attacks and development of amyloidosis

Case 2: DC

- 66-year-old gentleman with a history of GERD who presents for consultation regarding cough and fatigue
  - Reports a history of recurrent bronchitis (4 long bouts over 2 years)
  - Most recently was diagnosed with bronchitis in 6 months prior to presentation but symptoms did not improve with antibiotics
  - Cough described as non-productive fits of coughing throughout the day. He is typically able to sleep at night.
- SH: 15 pack-year history of cigarettes—quit 30 years ago
- MEDS: Ranitidine plus numerous supplements

DC—Chronic cough

JOHNS HOPKINS MEDICINE

Common causes

- Post-nasal drip
- Asthma
- GERD
- Post-infectious cough syndrome
- Medications: ACE inhibitors

Less common causes

- Bronchiectasis
- Chronic bronchitis
- Nonasthmatic eosinophilic bronchitis
- Bronchogenic carcinoma
- Interstitial lung disease
- Occult heart failure
- Occult aspiration

DC-Review of records

Blood work

ESR	**90 mm/hr**
WBC and Hgb	Normal
Plt	**357K/cu mm**
AST	Normal
ALT	**44 U/L**
Alkaline phosphatase	**197 U/L**

Other tests

- Chest x-ray and CT of chest unremarkable
- FEV1/FVC 112% predicted with normal flow volume loops
- RUQ ultrasound no abnormalities

DC—More history

- Patient reported that in addition to antibiotics, he had been put on varying doses of prednisone over the previous 6 months, during which time his symptoms do improve
- Denied fevers, chills, nausea, vomiting, hearing or vision changes, or weight loss
- Upon questioning, developed frontal headaches that radiate to the top and back of his skull about 2 months ago
  - “Eyeballs feel heavy”
- MRI of head done 3 weeks prior to presentation showed only mild periventricular white matter changes

DC—Physical exam

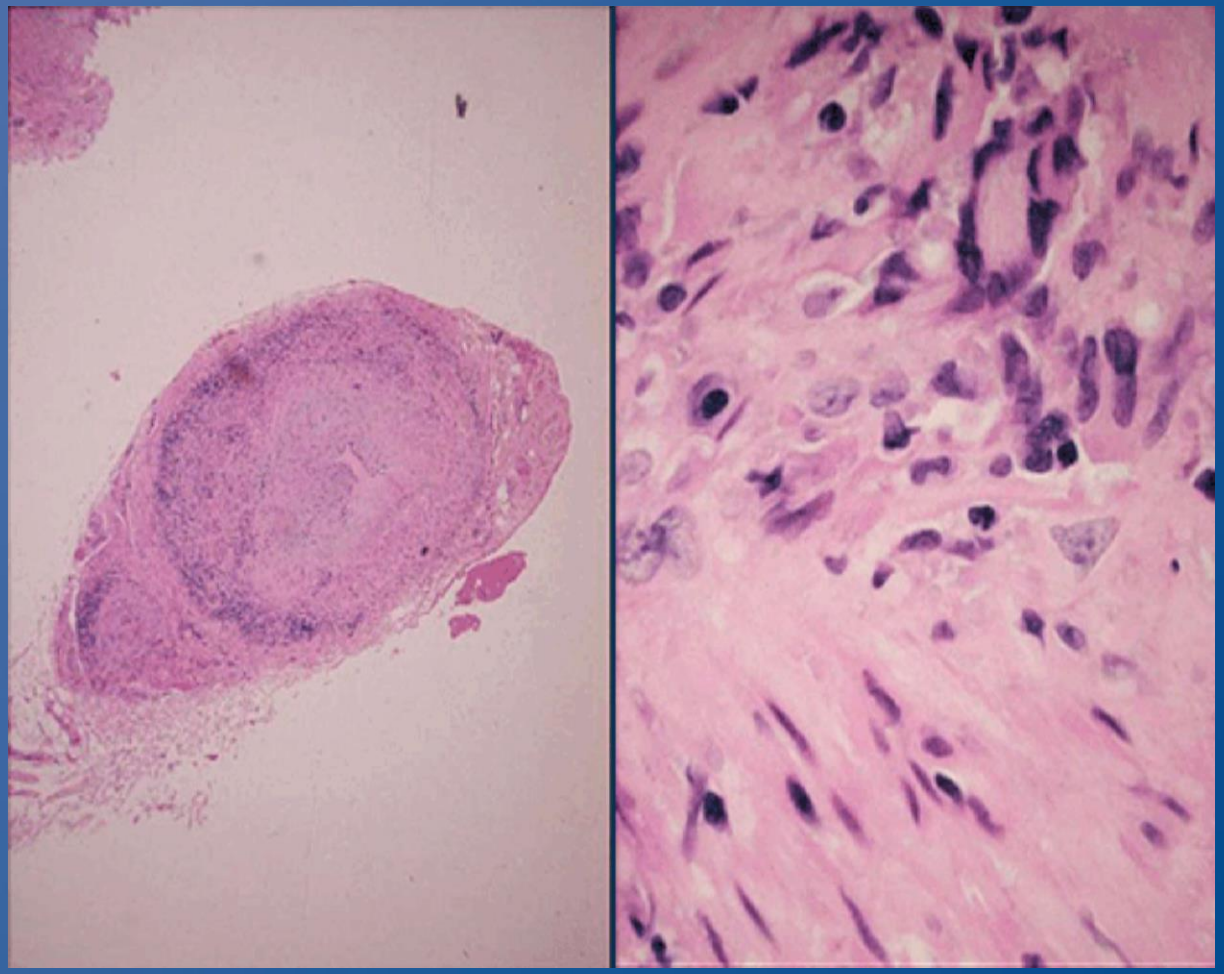
- VS: Temperature 97.2, pulse 90, respiratory rate 20, blood pressure 150/84, weight of 157 lbs
- GA: Pleasant gentleman in no acute distress
- HEENT: No papilledema. No sinus tenderness. No temporal artery prominence or tenderness
- Neck: No JVD, lymphadenopathy, or thyromegaly
- Chest: Clear, no wheezing or egophony. Good air movement
- Heart: No murmurs
- Neuro: No focal deficits

DC—Case summary

- 66-year-old man with 6 month history of cough and fatigue and 2 month history of frontal headaches which improve with prednisone
- Labs reveal elevation of inflammatory markers and alkaline phosphatase

- A diagnostic procedure was done

DC—Temporal artery biopsy



From: http://www.hopkinsmedicine.org/gec/studies/gca.html

Temporal arteritis—Classic presentations

Finding	Frequency, %
ESR > 40 mm/hr	94
Headache	77
Abnormal temporal artery	53
Jaw claudication	51
Constitutional symptoms	48
Polymyalgia rheumatica	34
Visual symptoms	29
Fever	26

From Hellmann, DB . JAMA 2002;2872997
Original data from Machado EBV, et al. Arthritis Rheum 1988;31:747

Temporal arteritis—Laboratory abnormalities

Lab	Frequency, %
Anemia (Hgb < 12 g/dl)	55
Thrombocytosis (>400K/cu mm)	49
Leukocytosis (>11K/cu mm)	28
Hypoalbuminemia (<3 g/dl)	28
Elevated alkaline phosphatase (>2x normal)	25

From: Gonzalez-Gay MA, et al. Medicine 2005; 84:279.

Temporal arteritis: Respiratory symptoms

- Include cough, sore throat, hoarseness, choking sensation, sore tongue, chest pain
- Estimated 9% of patients with TA have respiratory symptoms
- 4% have respiratory symptoms as their chief complaint

Larson TS, et al. Ann Int Med 1984;101:594-7

Back to DC

- Treated with 60 mg of prednisone
- Followed up with local rheumatologist and did well

Learning points

1. Cough and respiratory symptoms can be manifestations of temporal arteritis and can rarely be the presenting symptom
2. Alkaline phosphatase is frequently elevated in cases of TA

THANK YOU