CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 2-2024: A 57-Year-Old Woman with Melanoma and Fever

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PRESENTATION OF CASE

Dr. Matthew L. Meizlish (Medicine): A 57-year-old woman with resected stage IIIC cutaneous melanoma was admitted to this hospital because of fever.

The patient had been in her usual state of health until 4 months before the current admission, when bleeding developed from a lesion on the right side of the scalp. After evaluation by her primary care physician, she was referred to a surgical clinic at another hospital; examination of a skin-biopsy specimen revealed ulcerated melanoma with positive margins. The patient was referred to the oncology clinic of this hospital.

Three months before the current admission, a wide local excision of the scalp lesion and a neck lymph-node dissection were performed; examination of the specimens revealed metastatic melanoma in 2 of 26 lymph nodes. A diagnosis of stage IIIC melanoma was made. Molecular profiling identified the *BRAF* V600E mutation, and treatment with adjuvant therapy was planned to begin after the patient had recovered fully from surgery.

One month before the current admission, the patient was evaluated in the oncology clinic for initiation of treatment with a combination of dabrafenib (a BRAF inhibitor) and trametinib (a MEK inhibitor) as targeted therapy for melanoma. She felt well, and the surgical wound had healed. Laboratory test results are shown in Table 1. Treatment with dabrafenib and trametinib was started.

One day after the initiation of treatment with dabrafenib and trametinib, fever and nausea developed. Dabrafenib and trametinib therapy was temporarily discontinued, and treatment with acetaminophen and ibuprofen was started. Fever and nausea resolved after 1 day, and treatment with acetaminophen and ibuprofen was stopped. Once the patient had 1 day without recurrent fever after the antipyretic medications had been stopped, treatment with dabrafenib and trametinib was resumed.

Two weeks before the current admission, fever recurred. The patient was evaluated at the other hospital. The blood levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, and alkaline phosphatase were normal, as were the complete blood count and the results of tests of kidney function. Treatment with dabrafenib and trametinib was again stopped, and treatment with

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Table 1. Laboratory Data.*

Variable	Reference Range, Adults†	1 Mo before This Admission, Oncology Clinic, This Hospital	On Admission, This Hospital	Hospital Day 5, This Hospital
Blood				
White-cell count (per μl)	4500–11,000	3810	5190	3430
Differential count (per μl)				
Neutrophils	1800–7700	1810	4560	2720
Lymphocytes	1000–4800	1490	90	460
Monocytes	200–1200	450	—	150
Eosinophils	0–900	20	—	60
Basophils	0–300	30	—	—
Hemoglobin (g/dl)	13.0–16.0	13.0	12.9	9.4
Hematocrit (%)	37.0–49.0	40.6	38.9	27.2
Platelet count (per μl)	150,000–400,000	207,000	87,000	99,000
Prothrombin time (sec)	11.5–14.5	—	16.7	14.3
Prothrombin-time international normalized ratio	0.9–1.1	—	1.4	1.1
Activated partial-thromboplastin time (sec)	22.0–36.0	—	47.9	27.2
D-dimer (ng/ml)	0–500	—	>10,000	3457
Fibrinogen (mg/dl)	150–400	—	135	153
Sodium (mmol/liter)	135–145	138	131	138
Potassium (mmol/liter)	3.4–5.0	4.2	3.8	3.3
Chloride (mmol/liter)	98–108	109	97	107
Carbon dioxide (mmol/liter)	23–32	22	19	22
Urea nitrogen (mg/dl)	8–25	19	42	13
Creatinine (mg/dl)	0.60–1.50	0.86	2.73	1.07
Glucose (mg/dl)	70–110	99	118	99
Albumin (g/dl)	3.3–5.0	4.3	3.6	2.3
Total protein (g/dl)	6.0–8.3	6.6	6.6	4.9
Aspartate aminotransferase (U/liter)	9–32	30	190	407
Alanine aminotransferase (U/liter)	7–33	19	62	138
Alkaline phosphatase (U/liter)	30–100	76	173	510
Total bilirubin (mg/dl)	0.0–1.0	0.2	1.9	2.6
Lipase (U/liter)	13–60	—	42	—
Lactate dehydrogenase (U/liter)	110–210	—	285	658
Lactic acid (mmol/liter)	0.5–2.0	—	1.0	0.8
Creatine kinase (U/liter)	40–150	—	1679	—
Urine				
Color	Yellow	—	Yellow	—
Clarity	Clear	—	Turbid	—
pH	6.0	—	5.5	—
Specific gravity	1.012	—	1.013	—

Table 1. (Continued.)

Variable	Reference Range, Adults†	1 Mo before This Admission, Oncology Clinic, This Hospital	On Admission, This Hospital	Hospital Day 5, This Hospital
Glucose	Negative	—	Negative	—
Ketones	Negative	—	Negative	—
Leukocyte esterase	Negative	—	Negative	—
Nitrite	Negative	—	Negative	—
Blood	Negative	—	2+	—
Protein	Negative	—	1+	—
Red cells (per high-power field)	—	—	0–2	—
White cells (per high-power field)	—	—	0–10	—

* To convert the values for urea nitrogen to millimoles per liter, multiply by 0.357. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the values for bilirubin to micromoles per liter, multiply by 17.1. To convert the values for lactic acid to milligrams per deciliter, divide by 0.1110.

† Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.

acetaminophen and ibuprofen was started. Fever and nausea resolved after 1 day, and treatment with acetaminophen and ibuprofen was stopped. Once the patient had 1 day without recurrent fever after the antipyretic medications had been stopped, treatment with dabrafenib and trametinib was again resumed.

Four days before the current admission, fever recurred. The patient was again evaluated at the other hospital. Results of liver tests and kidney-function tests were again normal, as was the complete blood count. Treatment with dabrafenib and trametinib was again stopped, and treatment with acetaminophen and ibuprofen was initiated. Daily fevers persisted for 4 days, and the patient was advised to present to the emergency department of this hospital for evaluation.

On evaluation, the patient reported fatigue that had started 1 month earlier and had gradually increased in severity, as well as light-headedness when standing from a seated position. She also reported intermittent vomiting, loose stools, and pain in the right upper quadrant that increased after eating but no diarrhea or dysuria. She had a dry cough without shortness of breath.

Other medical history included carpal tunnel syndrome that had been treated with carpal tunnel release surgery. The patient had no known drug allergies. She worked as a nurse and lived with her husband and two adult children in a coastal region of New England. She did not drink alcohol, smoke cigarettes, or use illicit drugs. Her father had hyperthyroidism; her mother had hypertension, diabetes mellitus, and cerebrovascular disease.

The temporal temperature was 40.2°C, the blood pressure 85/53 mm Hg, the pulse 108 beats per minute, and the oxygen saturation 94% while the patient was breathing ambient air. She was diaphoretic and appeared ill. The mucous membranes were moist, and no lesions were present in the oropharynx. The heart sounds were regular, with no murmurs, and the lungs were clear on auscultation. There was mild tenderness in the right upper quadrant. No rash was present.

The white-cell count was 5190 per microliter (reference range, 4500 to 11,000); 20% of the cells were bands (reference range, 0 to 10), and 10% were metamyelocytes (reference value, 0). The platelet count was 87,000 per microliter (reference range, 150,000 to 400,000). The blood level of creatinine was 2.73 mg per deciliter (241 μmol per liter; reference range, 0.60 to 1.50 mg per deciliter [53 to 133 μmol per liter]), AST 190 U per liter (reference range, 9 to 32), ALT 62 U per liter (reference range, 7 to 33), and alkaline phosphatase 173 U per liter (reference range, 30 to 100). Tests of a nasopharyngeal swab for adenovirus, human rhinovirus and enterovirus, influenza virus types A and B, parainfluenza virus types 1 through 4, respiratory syncytial virus, and

severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were negative. A blood specimen was obtained for culture. Other laboratory test results are shown in Table 1. Imaging studies were obtained.

Dr. Jiyoon Kang: Ultrasonography of the right upper quadrant (Fig. 1A and 1B) revealed cholelithiasis without evidence of cholecystitis or biliary ductal dilatation. Computed tomography (CT) of the chest, abdomen, and pelvis (Fig. 1C through 1F), performed without the administration of intravenous contrast material, revealed findings suggestive of hepatic steatosis, pulmonary edema, small bilateral pleural effusions, subsegmental linear atelectasis, and bilateral lung nodules that were similar in appearance to those seen on staging CT performed 1 month earlier.

Dr. Meizlish: Intravenous fluids were administered, and the blood pressure improved; empirical treatment with vancomycin, cefepime, metronidazole, and azithromycin was initiated. The patient was admitted to the hospital.

On hospital day 2, fever and nausea resolved. There was no vomiting or loose stools. However, pain in the right upper quadrant had worsened. On hospital day 3, blood cultures were without growth, and treatment with vancomycin, cefepime, metronidazole, and azithromycin was discontinued. The patient remained afebrile. On hospital day 5, the blood level of AST was 407 U per liter, ALT 138 U per liter, and alkaline phosphatase 510 U per liter. Other laboratory test results are shown in Table 1.

A diagnostic test was performed.

DIFFERENTIAL DIAGNOSIS

Dr. Amir M. Mohareb: I was involved in the care of this patient, and I am aware of the final diagnosis. The patient had recently begun adjuvant therapy with combination BRAF–MEK inhibitors for resected stage IIIC melanoma. Her early treatment course was complicated by two episodes of fever that rapidly resolved after brief discontinuation of treatment with BRAF–MEK inhibitors. The current admission is characterized by an acute illness with high fevers that persisted for 4 days after discontinuation of treatment with BRAF–MEK inhibitors. She also had hypotension, acute kidney injury, and acute liver injury.

In this case, defining a clinical syndrome and developing a differential diagnosis is challenging because the patient presented with numerous abnormalities involving multiple organ systems. The challenge is in selecting the clinical problems that are most pertinent to the cause of the underlying disease, rather than abnormalities that are consequences of the underlying disease or are incidental findings. If the clinical problem that is selected is too nonspecific (e.g., fatigue), the differential diagnosis becomes unmanageable. On the other hand, if the syndrome selected is too specific, there is a risk of focusing too narrowly and missing the underlying disease. For this patient, I will focus on the clinical syndrome of fever.

In many patients who present with fever, an infectious cause can be rapidly identified on the basis of a set of localizing symptoms and findings on diagnostic testing (e.g., the presence of cough and lung opacities). In addition, an organism may be quickly identified by means of microbiologic testing, completing the diagnostic evaluation. However, in this patient, no diagnostic imaging findings or microbiologic studies pointed to a specific infectious cause of fever. Therefore, I will approach her case systematically by considering the time course of the fevers, the host immune system, the environment and exposures, and key diagnostic findings.

TIME COURSE OF FEVERS

When evaluating the time course of fevers, I consider the severity (i.e., maximum temperature), duration, and pace of illness. In this patient, fever developed 4 weeks before the current admission and 1 day after starting BRAF–MEK inhibitors for the treatment of melanoma.[1] These therapies are known to cause treatment-related pyrexia.[2,3] This patient had three discrete febrile episodes after beginning treatment with BRAF–MEK inhibitors, the last of which persisted and progressed despite the discontinuation of these therapies. A key question was whether the third febrile episode leading to hospitalization was part of a syndrome that had lasted for 4 weeks and was consistent with treatment-related pyrexia from BRAF–MEK inhibitor therapy or whether it was an acute illness that was separate from the previous episodes. When the patient initially presented to the emergency department, she was