CLINICAL PROBLEM-SOLVING

Consumed with Inflammation

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In this Journal *feature, information about a real patient is presented in stages (boldface type) to an expert clinician, who responds to the information by sharing relevant background and reasoning with the reader (regular type). The authors' commentary follows.*

A 60-year-old woman with stage II triple-negative breast cancer presented to the emergency department with a weeklong history of fevers, rigors, malaise, nonproductive cough, and nausea. She reported intermittent lightheadedness, headaches, and neck pain when febrile but no sore throat, rhinorrhea, shortness of breath, vomiting, abdominal pain, or dysuria. She noted no recent travel or sick contacts. Two months before presentation, she completed neoadjuvant carboplatin, paclitaxel, and doxorubicin and then, 1 month before presentation, underwent lumpectomy of the left breast and sentinel-lymph-node biopsy. She had also been treated as part of a clinical trial with multiple cycles of pembrolizumab (first dose, 6 months before presentation; last dose, 6 days before presentation). Although she had had transient neutropenia from chemotherapy, her white-cell counts had normalized after her last cycle. Postoperatively, mild tenderness and swelling around her left axilla had developed without systemic signs of infection; computed tomographic (CT) imaging was consistent with an uncomplicated seroma. In the days leading up to this presentation, her tenderness in this area had resolved.

In this patient with chemotherapy-related immunocompromise, I am most concerned about an infection causing the fever and associated symptoms. Her cough suggests the possibility of upper or lower respiratory tract infection. Given her residual axillary seroma, a superimposed soft-tissue infection could also be driving her fevers, although the absence of worsening tenderness in this area makes this less likely. Pembrolizumab-associated inflammatory conditions, including cytokine release syndrome or hemophagocytic lymphohistiocytosis (HLH), should also be considered. Cancers can also cause fever, but this is unlikely with breast cancer.

The patient was not taking any medications, nor did she have any allergies to medications. She lived in a suburban part of the northeastern United States without any animal exposures. She enjoyed hiking and biking in outdoor areas but reported no recent insect bites. Her son, with whom she lives, had recently traveled to the United Arab Emirates but did not report any infectious symptoms. She had not ingested any raw, unpasteurized, or imported food products but reported recently handling raw goat and lamb meat bought from a local butcher.

Her exposure to raw goat and lamb meat arouses concern for infection with brucella or *Toxoplasma gondii*. Although she has no known bites, she lives in a region where tickborne infections (borrelia, babesia, anaplasma, and ehrlichia) are endemic, and these should be considered. Given her cough, respiratory infections, including coronavirus disease 2019 (Covid-19), also warrant consideration.

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CME

On physical examination, the patient appeared comfortable. The oral temperature was 38.9°C, heart rate 120 beats per minute, blood pressure 100/63 mm Hg, and oxygen saturation 99% while she was breathing ambient air. Her neck was supple, and there was no cervical, submandibular, or supraclavicular lymphadenopathy. No oral mucosal lesions were present. A cardiac examination was notable for tachycardia without murmurs, rubs, or gallops. The lungs were clear to auscultation. The abdomen was soft, nondistended, and nontender to palpation without hepatosplenomegaly. She was alert and oriented and had no focal neurologic deficits. A skin examination was notable for a small, erythematous, tender but nonfluctuant papule on her scalp (Fig. 1) and a well-healing incision in the left axilla at her lumpectomy site without overlying erythema, fluctuance, or tenderness to palpation.

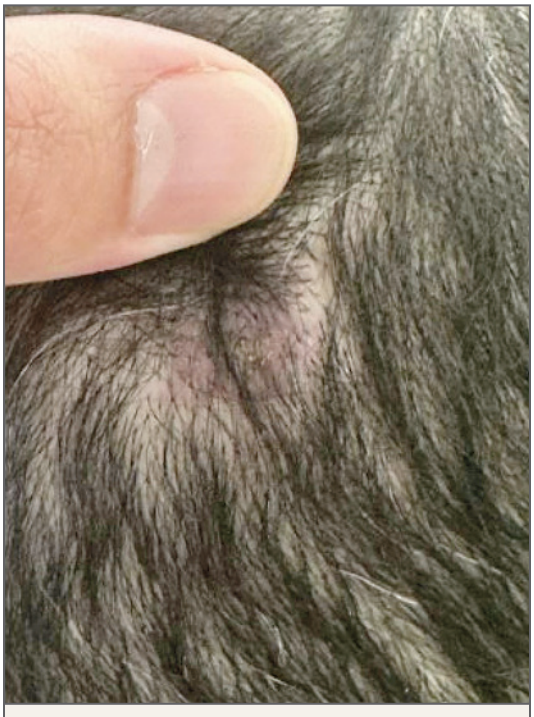

Figure 1. Scalp Lesion.
A small (<1 cm in diameter), mildly erythematous, and tender but nonfluctuant papule was present on the scalp and had been present for 4 days. The patient was not aware of this lesion until it was identified on the presenting physical examination.

Her normal pulmonary examination is reassuring but insensitive to rule out a respiratory infection. The absence of erythema or tenderness in the axillary region argues against a postoperative abscess, although radiographic imaging with either ultrasonography or CT is warranted. The differential for her scalp lesion, which was incidentally found, is broad. The papular appearance of the lesion without obvious fluctuance or purulent drainage is less consistent with cellulitis or abscess. Although the appearance is not typical of borrelia-associated erythema migrans, this should remain in the differential diagnosis. Reactivation of varicella–zoster virus infection should be considered in this immunocompromised patient and could have this appearance despite the lack of symptoms. Malignant etiologic factors such as cutaneous metastases or Sweet syndrome should also be considered, although the latter is more often associated with numerous lesions rather than one isolated lesion, as in this case.

The white-cell count was 1860 per microliter, hemoglobin level 9.2 g per deciliter, and platelet count 66,000 per microliter. (These values were 4670 per microliter, 11.2 g per deciliter, and 162,000 per microliter, respectively, 1 month earlier.) The neutrophil count was 1390 per microliter (normal range, 1920 to 7600), lymphocyte count 350 per microliter (normal range, 720 to 4100), and monocyte count 100 per microliter (normal range, 160 to 1100). A comprehensive metabolic panel; coagulation studies, including prothrombin time (expressed in the international normalized ratio), partial-thromboplastin time, and fibrinogen level; and lactate level were unremarkable. Nasopharyngeal polymerase-chain-reaction (PCR) testing for Covid-19, influenza, parainfluenza, adenovirus, and respiratory syncytial virus was negative. Sputum and throat cultures were negative. Blood cultures were obtained. The C-reactive protein level was 248.9 mg per liter (normal value, <3.0), and the erythrocyte sedimentation rate was 34 mm per hour (normal value, <30). Testing for antibodies against *Bordetella pertussis* and *Mycoplasma pneumoniae* was negative. Serologic testing for brucella and toxoplasma was negative. Serum PCR studies for Epstein–Barr virus, parvovirus, cytomegalovirus, and toxoplasma

were also negative, as were tests for beta-D-glucan and galactomannan. Urinalysis showed trace bacteria without red or white cells; urine culture grew less than 10,000 colony-forming units (CFU) per milliliter of corynebacterium species and 10,000 to 50,000 CFU per milliliter of lactobacillus species.

Although this patient has neutropenia (defined as an absolute neutrophil count of <1500 cells per microliter), her level of neutropenia is mild (1000 to 1500 cells per microliter), which does not substantively increase her risk of infection. However, infection remains a concern, and CT imaging would be helpful to evaluate her respiratory symptoms and axillary tenderness.

CT of the chest, abdomen, and pelvis with intravenous contrast was performed and revealed a persistent fluid collection in the left axillary space (Fig. 2A) where the patient had undergone her lumpectomy and axillary lymph-node biopsy. Although it was slightly larger than on previous imaging, there were no features to suggest a superimposed abscess. There was also mild splenomegaly (Fig. 2B) but no other evidence of any inflammatory or infectious process.

The most notable finding in this patient's CT imaging was the fluid collection around the site of her lymph-node dissection. Postoperative fluid collections can be composed of serous fluid filling a new anatomical vacuum left behind by surgery or can reflect infection. Radiologic findings suggestive of an infection were absent in this case, and there was no localized pain or tenderness. Splenomegaly is a nonspecific finding and can be seen in infectious, neoplastic, or inflammatory conditions. No other findings suggest an underlying hematologic cancer. Infection should remain highest in the differential diagnosis; an inflammatory disorder is also possible, especially given her recent exposure to pembrolizumab.

Intravenous antibiotic therapy with vancomycin and cefepime was initiated on admission. The patient remained febrile, and on day 3 of admission, she was switched from cefepime to piperacillin–tazobactam for improved anaerobic coverage, and doxycycline was added for empirical treatment of tickborne illnesses. Despite broad-spectrum antibiotics, the patient continued to have fevers, and on hospital day 4, symptomatic hypotension developed.

Given the ongoing fevers despite a negative infectious workup and the absence of new medications or evidence of cancer on CT imaging, the two most likely diagnoses are HLH or cytokine release syndrome, both of which are recognized to occur after immunotherapy with pembrolizumab. Because cytokine release syndrome typically occurs shortly after initiation of immunotherapy and this patient presented after having

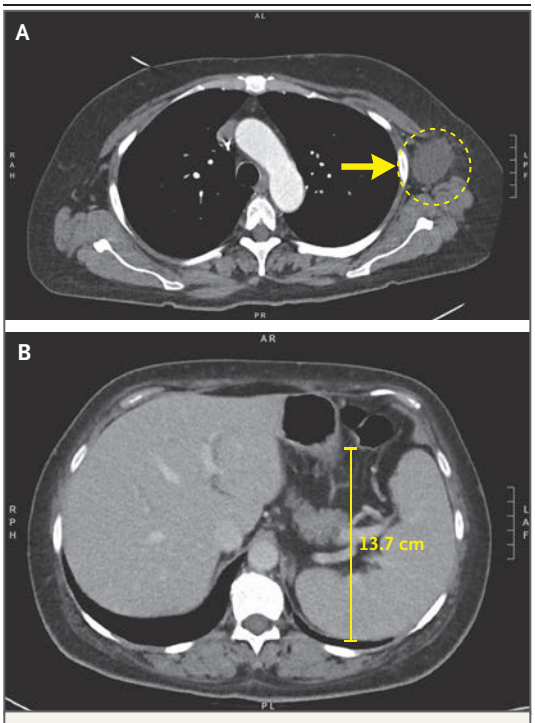

Figure 2. Computed Tomography of the Chest, Abdomen, and Pelvis with Intravenous Contrast.

Panel A shows a fluid collection measuring 4 cm by 3 cm (arrow) in the left axillary space where the patient had undergone her lumpectomy and axillary lymph-node biopsy. There was no thickening of the wall around the fluid, enhancement with contrast, internal gas loculations, or fat stranding to suggest a superimposed infection. Panel B shows that the spleen was enlarged at 13.7 cm (abnormal, >13.0 cm in the craniocaudal dimension); in previous imaging a month earlier, the size of the spleen was less than 11.5 cm.

received several cycles of pembrolizumab, the timing is more consistent with HLH.

The patient's hypotension resolved with intravenous fluid boluses. Her white-cell count and hemoglobin level continued to decrease, with lows of 1010 per microliter and 7.0 g per deciliter, respectively. Additional laboratory testing showed a ferritin level of 37,956 micrograms per liter (normal range, 13 to 150), a triglyceride level of 296 mg per deciliter (3.3 mmol per liter; normal range, 35 to 150 mg per deciliter [0.4 to 1.7 mmol per liter]), a fibrinogen level of 222 mg per deciliter (normal range, 200 to 400), a soluble CD25 level of 4268.1 pg per milliliter (normal range, 175.3 to 858.2) by enzyme-linked immunosorbent assay, and an interleukin-6 level of 56.2 pg per milliliter (normal value, <7.1). Flow cytometry and molecular testing did not show evidence of a hematologic cancer.

The combination of fever, splenomegaly, cytopenias, hypertriglyceridemia, hyperferritinemia, and elevated level of soluble CD25 (a soluble form of the interleukin-2 receptor alpha chain) is consistent with a diagnosis of HLH. Whether the CD25 level meets diagnostic criteria is uncertain, because established criteria relied on a different functional assay, and there is no accepted conversion factor. Nonetheless, in this clinical context with the other features present, the diagnosis of HLH appears certain.

On day 5, intravenous methylprednisolone (1 mg per kilogram of body weight daily) was initiated and resulted in immediate resolution of the patient's fevers, easing of her cytopenias, and reduction in the ferritin level. By day 8, blood cultures remained negative, and doxycycline was stopped after PCR tests for babesia, borrelia, ehrlichia, and anaplasma were negative. On day 9, she was transitioned to oral prednisone (100 mg daily) and discharged on hospital day 11 with a plan to slowly taper her dose of prednisone by 10 mg weekly. She continued to do well clinically, and the decision was made to discontinue pembrolizumab. Additional scalp lesions developed after discharge that were biopsied and consistent with shingles, for which she was treated with valacyclovir.

Although varicella can be a trigger of HLH, it typically occurs as a result of primary varicella virus infection or after vaccination. In addition, given the clinical improvement before valacyclovir and the appearance of additional lesions during the receipt of glucocorticoids, reactivation of varicella virus infection is unlikely to be the trigger of her HLH and pembrolizumab remains the likely cause.

COMMENTARY

This patient presented with fever and neutropenia that persisted despite broad-spectrum antibiotics without evidence of active infection. In the context of recent treatment with pembrolizumab, splenomegaly, and other serologic markers, she ultimately received a diagnosis of pembrolizumab-associated HLH, which responded rapidly to glucocorticoid therapy.

HLH is a rare hematologic condition characterized by inappropriate activation of the immune system leading to persistent macrophage activity.[1] The resulting pathologic inflammatory response can lead to distributive shock and multiorgan failure in severe cases. Although it is traditionally diagnosed clinically, multiple scoring systems are available to aid in diagnosis.[2,3] The HLH-2004 criteria, a commonly used system, indicate that a diagnosis can be made if a patient either has a documented associated genetic mutation or fulfills five of the eight following criteria: fever; splenomegaly; cytopenias affecting at least two blood lineages; hypertriglyceridemia or hypofibrinogenemia; hemophagocytosis in bone marrow, spleen, or lymph nodes; low or no natural killer (NK)–cell activity; hyperferritinemia; and an elevated soluble CD25 level.[3] None of these features individually is specific for HLH. Moreover, a recent study showed that exclusion of NK-cell activity from the HLH-2004 criteria did not reduce diagnostic accuracy, which raises questions about its relevance for diagnosis.[4]

These criteria directly stem from the pathogenesis of the disease, which involves inappropriate activation of immune cells (including T lymphocytes and macrophages), leading to proinflammatory cytokine release and fever. The excessive inflammation suppresses the bone marrow, which leads to cytopenias. Moreover, the inflammatory

environment, particularly the increase in tumor necrosis factor α (TNF-α), is thought to suppress lipoprotein lipase (which normally breaks down triglycerides), leading to hypertriglyceridemia. Finally, macrophages also secrete enzymes that promote fibrin degradation and synthesize excessive ferritin, which drives the remainder of the abnormalities in laboratory measures.[5,6] Other markers that are associated with HLH include elevated levels of CXCL9 (a marker of interferon-γ production) and interleukin-18.[1,6]

HLH can be classified into primary or secondary subtypes. Primary or familial HLH manifests predominantly in childhood and is the result of mutations in genes involved in T-cell or NK-cell cytotoxicity or inflammasome activity, such as perforin-1 (*PRF1*), MUNC13-4 (*UNC13D*), MUNC18-2 (*STXBP2*), and syntaxin-11 (*STX11*).[1] Secondary HLH occurs in association with a number of underlying conditions, such as cancer, infection, and autoimmune disease.[1] Among a nationally representative sample of adult patients admitted nonelectively with HLH, cancer was the most common associated condition, with lymphomas predominant.[7] Infections were next most frequent, most commonly those due to viruses (and among these, most often Epstein–Barr virus or cytomegalovirus), although infections with intracellular pathogens such as fungi, mycobacteria, and parasites were also reported. A particularly glucocorticoid-responsive variant of secondary HLH has also been associated with systemic autoimmune disease (termed macrophage activation syndrome in this context) such as systemic lupus erythematosus, adult-onset Still's disease, and systemic juvenile idiopathic arthritis in children.[1,3,5,8] Studies of HLH in the absence of cancer have identified heterozygous hypofunction variants in canonical genes that may be contributory.[9,10]

HLH that is triggered by checkpoint inhibitor therapies is a rare but increasingly appreciated entity[11]; a World Health Organization database recently included 681 reports of such cases (231 reports for nivolumab, 179 for pembrolizumab, 169 for ipilimumab, 90 for atezolizumab, and 12 for durvalumab).[12] This condition is one of a wide range of reactions caused by checkpoint inhibitor–mediated iatrogenic overactivation of the immune system, including cytokine release syndrome and organ-specific toxic effects. The driving pathophysiological feature of immune checkpoint inhibitor–associated HLH is disinhibition of costimulatory molecules that usually suppress T-cell activation. Although this is the desired effect of immune checkpoint inhibitors, disinhibition of T-cell activation can lead to an inappropriate release of inflammatory cytokines (such as interleukin-6, TNF-α, and interferon-γ, similar to cytokine release syndrome).[13] Unlike cytokine release syndrome, which usually occurs within days after immunotherapy, immune checkpoint inhibitor–associated HLH typically occurs later. In a case series of 18 patients, the median time of onset was 6.7 weeks (ranging from 3 to 16 weeks) after treatment initiation.[11]

There are limited data on appropriate management of immune checkpoint inhibitor–associated HLH. In the absence of randomized, controlled trials, the data largely derive from case series or are extrapolated from studies in other forms of secondary HLH. Management of immune checkpoint inhibitor–associated HLH typically includes stopping immunotherapy and treating with high-dose glucocorticoids or agents such as anakinra (interleukin-1 receptor antagonist) and ruxolitinib (Janus kinase 1 and 2 inhibitor), with consideration of low-dose etoposide in refractory cases.[13,14] Given the elevation of the interferon-γ level, some experts suggest a possible role for empalumab (anti–interferon-γ antibody), which appeared effective in an open-label study involving children with primary HLH.[15]

This patient's fevers, splenomegaly, and high levels of inflammatory markers after treatment with pembrolizumab were ultimately recognized to be manifestations of HLH associated with checkpoint inhibitor therapy. Although this clinical entity is rare, this case highlights the importance of considering systemic inflammatory syndromes as causes of fever in patients with cancer and underscores an underrecognized manifestation of immunotherapy toxicity.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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