A 33-year-old woman was admitted to our medical center because of progressive, diffuse, constant, and non-radiating abdominal pain that had started 6 months earlier. The pain was not accompanied by diarrhea, constipation, or vomiting, and the patient did not notice any blood or mucus in her stool. The pain was not related to food intake and could not be relieved by defecation. The patient also presented with a troublesome dry cough, general weakness, and fatigue. There were no observations of fever, night sweats, or unintentional weight loss.

Her past medical history was significant for upper abdominal pain at age 17 years that was different in character and severity from the present one. At that time, a gastroscopy was performed and a *Helicobacter pylori* infection was diagnosed. After treatment with the usual triple therapy of clarithromycin, amoxicillin, and omeprazole, her pain stopped and a breath test confirmed eradication of the bacterium. Otherwise she was healthy and took no medications.

She had been married for the last 8 years and was sexually active with her husband with the use of contraceptives. At age 27 years she underwent a Cesarian section due to a breech position of the fetus. She had no other pregnancies. Her menstrual period was regular with a 30-day interval. Her family medical history included incomplete information about her mother who experienced prolonged abdominal pain, which was never investigated.

Examination in the emergency department revealed normal vital signs. The patient seemed healthy and alert. Physical examination was remarkable for a palpable lymph node (1 cm) in the right axilla and diffused moderate abdominal tenderness. Laboratory results demonstrated normal blood count with slight lymphopenia. Blood electrolytes, as well as kidney and liver function tests, were all within normal limits. The patient exhibited hypergammaglobulinemia without a monoclonal peak on protein electrophoresis. Uric acid was mildly elevated. Beta human chorionic gonadotropin was negative and a urine dipstick did not disclose any abnormalities. Her initial C-reactive protein level (CRP) and erythrocyte sedimentation rate (ESR) were both slightly elevated.

1. Based on the clinical scenario, which of the following diseases is the most likely in this patient?
   a. Crohn’s disease
   b. Lymphoma
   c. Tuberculosis
   d. Endometriosis
   e. Sarcoidosis

Abdominal pain is a common problem. Most patients have a benign self-limited disease, and the initial goal of evaluation is to identify those patients with a serious etiology that may require intervention. Using a systemic approach is crucial, especially when encountering a patient with subacute unspecific symptoms, signs, and laboratory results.

Abdominal pain and fatigue are common manifestations of Crohn’s disease (CD). However, prolonged diarrhea or constipation with or without gross bleeding, weight loss, fever, and extra intestinal symptoms are the hallmarks of the disease and were absent in our patient.

Patients with indolent lymphoma, either Hodgkin or non-Hodgkin, can initially present with painless peripheral lymphadenopathy and abdominal pain. Although *H. pylori* infection is strongly associated with the development of primary gastric lymphoma, eradication of the bacterium reduces the risk and localized epigastric pain, weight loss, and vomiting are expected. In addition, secondary symptoms (systemic symptoms of fever, night sweats, and weight loss), hepatosplenomegaly, and laboratory abnormalities like elevated lactate dehydrogenase or cytopenia are common features of nodal lymphoma.

The diagnosis of miliary tuberculosis can be challenging due to nonspecific clinical symptoms and signs. The disease can cause cough, fatigue, abdominal pain, and isolated lymphadenopathy but it should be suspected in patients with a relevant epidemiologic or exposure history including clinical manifestations such as fever and night sweats.
Most women with endometriosis demonstrate, during their reproductive years, pelvic-abdominal pain (including dysmenorrhea and dyspareunia) and infertility. In addition, lymphadenopathy is not one of the symptoms of this gynecological disease.

Finally, fatigue, cough, peripheral lymphadenopathy, and indolent abdominal pain may support the diagnosis of sarcoidosis. Although sarcoidosis usually presents with respiratory symptoms that are frequently accompanied by hilar adenopathy, systemic symptoms of the disease can involve all organ systems.

Interestingly, an abdominal computed tomography (CT) scan of our patient revealed mesenteric lymphadenopathy and multiple splenic and hepatic hypodense nodules. In addition, sub-pleural nodules and pleuro-pulmonary adhesions were found. However, a chest X-ray did not display any abnormalities. Thus, a chest CT was performed to more accurately define these peculiar findings. Consequently, the scan exhibited bilateral hilar adenopathy with calcifications and a “tree in bud” appearance, consisting of small pulmonary nodules distributed diffusely across both lungs.

2. Which of the following tests is less useful for the patient's diagnosis?
   a. Tuberculin skin test
   b. Fluorodeoxyglucose positron emission tomography (FDG-PET)
   c. Angiotensin converting enzyme (ACE) level
   d. Electrocardiogram
   e. Ophthalmologic examination

The abnormalities detected on CT scans are suggestive of sarcoidosis, tuberculosis, or lymphoma. Although our patient did not have the relevant epidemiologic or exposure history, a tuberculin skin test was performed because a positive test is strong evidence in favor of mycobacterial disease and diminished skin test reactivity is expected in sarcoidosis or lymphoma. As expected, the results of the tuberculin skin test in our patient were negative.

FDG-PET does not differentiate sarcoidosis from malignancy, as it may be positive in both and should not be performed routinely. However, ACE level is elevated in 75% of untreated patients with sarcoidosis. Although serum ACE has limited benefit as a diagnostic test, elevated levels can point toward a diagnosis of sarcoidosis. Indeed, the ACE levels in our patient were very high (85 units/L).

We suggest that a comprehensive initial evaluation should be performed in all sarcoidosis suspected patients. Consistent with this idea, an electrocardiogram must be part of any evaluation because sarcoidosis may involve the heart conducting system and cause heart block and even fatal arrhythmias. Furthermore, as ocular involvement of sarcoidosis may be asymptomatic but advanced, all patients should undergo an ophthalmologic examination. Our patient's electrocardiogram and ophthalmologic exams were normal.

3. Which findings are required for diagnosis of sarcoidosis in this patient?
   a. Elevated ACE levels, bronchoalveolar lavage with elevated CD4/CD8 ratio and pulmonary symptoms
   b. Bronchoalveolar lavage with elevated CD4/CD8 ratio pulmonary symptoms, and radiologic hilar lymphadenopathy
   c. Compatible clinical and radiographic manifestations, exclusion of other diseases that may present similarly, and histopathologic detection of non-caseating granulomas
   d. Compatible clinical and radiographic manifestations, exclusion of other diseases that may present similarly, and bronchoalveolar lavage with elevated CD4/CD8 ratio
   e. Pulmonary symptoms, radiologic hilar lymphadenopathy, and exclusion of other diseases that may present similarly

A definitive diagnostic test for sarcoidosis does not exist. Instead, the diagnosis of sarcoidosis requires three elements: compatible clinical and radiographic manifestations, exclusion of other diseases that may present similarly, and histopathologic detection of non-caseating granulomas. These elements are achieved by a comprehensive evaluation in all patients with suspected sarcoidosis, followed by a diagnostic procedure in most cases. Common presenting respiratory symptoms include cough, dyspnea, and chest pain. These symptoms are frequently accompanied by fatigue, malaise, fever, and weight loss. Bilateral hilar adenopathy and reticular opacities are common radiological findings. They are usually detected incidentally on routine chest radiographs prior to the development of symptoms. In general, involvement of more than one organ system is required for a diagnosis of sarcoidosis, although biopsy of a second site is not always needed. For example, the combination of non-caseating granulomas in one organ (e.g., skin, lung) and clinical evidence of sarcoid in another (e.g., hypercalcemia, bilateral hilar enlargement) would generally be sufficient for a diagnosis of sarcoidosis.

Serum ACE level has limited effectiveness as a diagnostic test for sarcoidosis. Other diseases associated with an elevated serum ACE include tuberculosis and Hodgkin's lymphoma [1]. Bronchoalveolar lavage can be used as an adjunctive measure to support the diagnosis of sarcoidosis by demonstrating a reduced number of CD8 cells, an elevated CD4/CD8 ratio, and an increased amount of activated T cells. Bronchoalveolar lavage is also used to exclude infections and malignancy as alternative diagnoses, but is not a sole diagnostic tool for sarcoidosis.

The patient was treated symptomatically in our department with fluids, metoclopramide, non-steroidal anti-inflammatory drugs, and papaverine. Because of the bilateral calcified hilar adenopathy observed on chest CT scan, a bronchoscopy was performed.
No macroscopic abnormal findings were viewed in the upper airways. Bronchoalveolar lavage demonstrated high levels of CD4 and CD4/CD8 ratio. CD3, CD8, and white blood cell count with differential were all at normal levels. Biopsies were taken for stains, cultures, and pathological examination. Ziehl–Neelsen stain for acid-fast bacilli was negative, as was periodic acid–Schiff stain for fungi. The pathology report described non-caseating granulomas in the interstitium, consisting of epithelioid histiocytes and multi-nucleated giant cells wrapped in hyaline fibrosis. As expected, the pathology report combined with the results of the bronchoalveolar lavage clinched the diagnosis of sarcoidosis.

Before deciding on treatment, we performed various additional tests on the patient. Pulmonary function tests did not reveal any restrictive or obstructive patterns. However, the patient exhibited breathing difficulty on exertion. Therefore, a cardiac echocardiography was performed, which was completely normal.

4. Which of the following initial treatments would be most appropriate in the management of this patient?
   a. Observation without therapy
   b. Budesonide 1600 µg twice daily
   c. Prednisone 40 mg daily
   d. Methotrexate 5 mg weekly
   e. Azathioprine 50 mg daily

Most patients with pulmonary sarcoidosis do not require treatment, as a high proportion have asymptomatic, non-progressive disease or experience a spontaneous remission. Inhaled glucocorticoids have been evaluated as treatment of pulmonary sarcoidosis, but results are conflicting. Budesonide (800–1600 µg twice daily) has been the most frequently used inhaled glucocorticoid [2]. Many clinicians advise a trial of inhaled glucocorticoids for sarcoidosis patients with only mild pulmonary symptoms. However, our patient also had concomitant extrapulmonary manifestion of the disease, which is an indication for systemic pharmaceutical treatment. Oral glucocorticoids are the most commonly used agents for the relief of these symptoms and for long-term control of sarcoidosis. Therapy is usually initiated with a daily prednisone oral dose of 0.3–0.6 mg/kg ideal body weight (usually 20–40 mg/day), depending on the severity of disease activity [2]. While the majority of patients respond to glucocorticoid therapy, some patients do not respond despite an adequate trial of therapy. These patients may be intolerant of glucocorticoids and are considered to be candidates for immunosuppressive therapy. Intensification of therapy for these patients typically involves immunosuppressive agents such as methotrexate or azathioprine [3].

Following consultation with a pulmonologist and rheumatologist in our hospital, and considering the patient’s lung involvement (stage 2, with bilateral hilar lymphadenopathy [BHL] and infiltrates), shortness of breath on exertion, and obvious symptomatic abdominal pain, we decided to start treatment with systemic steroids. Due to the patient’s young age and the known harmful effects of long term steroid use, we began treatment with 40 mg prednisone every other day.

It was recommended that the patient undergo periodic follow-up at our pulmonologist clinic, and her steroid dose tapered down and managed according to her clinical improvement, as well as her side-effect profile.

COMMENT

This clinical education case illustrates the difficulties in establishing a precise diagnosis when faced with a common disease accompanied clinically with uncommon manifestations. This case also poses a dilemma regarding the best approach to take to reach the correct diagnosis and treatment.

CLINICAL MANIFESTATIONS

Sarcoidosis is a multisystem granulomatous disorder of unknown etiology that affects individuals worldwide and is characterized pathologically by the presence of non-caseating granulomas in involved organs. It typically affects young adults and can involve all organ systems to a varying extent and degree. Sarcoidosis most frequently involves the lungs (95%), but up to 30% of patients also present extrapulmonary manifestations [Table 1] [4].

The most common sites of extrapulmonary disease include the skin (different from erythema nodosum), lymph nodes, and eyes. Less common sites are the reticuloendothelial system, musculoskeletal system, exocrine glands, heart, kidney, and central nervous system [Table 1]. Abdominal adenopathy presented in approximately 30% of patients with sarcoidosis. It can be found most commonly along the celiac axis, porta hepatis, para-aortic, and para-caval regions. Interestingly, differences were found between patients with sarcoidosis and lymphoma regarding the location and size of abdominal lymph nodes. In lymphoma, the nodes are involved significantly more frequent in the retrocruar area and are significantly larger [5].

Patients with sarcoidosis and hepatic involvement are usually asymptomatic. The most common symptoms associated with hepatic sarcoidosis are abdominal pain and pruritus. Serum liver function tests are abnormal in up to 35% of sarcoidosis patients, with the most common abnormality being an elevation of serum alkaline phosphatase.

Patients with splenic sarcoidosis are usually asymptomatic. The most common symptom of splenic sarcoidosis is left upper quadrant abdominal pain resulting from splenomegaly that causes stretching of the splenic capsule. Very rarely, hypersplenism and/or massive splenomegaly accompanying sarcoidosis may cause intractable pain or a reduction in cell lines, raising the
question of whether splenectomy should be recommended [6].

Involvement of abdominal viscera may mimic more common infectious or neoplastic conditions. In a case presented by Ben-Chetrit and colleagues in 2016 [7], a patient with low grade fever, splenomegaly, pancytopenia, and epitheloid granulomata found in bone marrow biopsies underwent splenectomy to establish sarcoidosis diagnosis. However, her final diagnosis was small B cell lymphocytic lymphoma, emphasizing the similarity between these two diseases.

Fatigue is a common symptom in patients with sarcoidosis, occurring in up to 80% of patients [Table 1]. The level of fatigue appears to be dependent on the presence of extrapulmonary sarcoidosis, that is, those with extrapulmonary disease exhibit higher levels of fatigue than those with only pulmonary sarcoid [8].

Accordingly, our young patient presented with abdominal pain, generalized weakness, and fatigue. Her abdominal CT revealed mesenteric lymphadenopathy and multiple splenic and hepatic hypodense nodules. It is reasonable to conclude that her diffused abdominal pain was the result of mesenteric lymphadenitis combined with hepatic and splenic abnormalities.

LABORATORY FINDINGS

Laboratory tests help to confirm the diagnosis of sarcoidosis, eliminate alternative diagnoses, assess involved organs, and estimate disease activity. Even normal results offer useful information. Cell blood count is usually normal, although a frequent lymphopenia is usually associated with disease activity. Anemia, neutropenia, or thrombocytopenia are rare in sarcoidosis and may be due to splenomegaly, bone marrow localization, or autoimmunity. Serum protein electrophoresis may be normal but often shows polyclonal hypergammaglobulinemia. It is crucial to exclude the possibility of granulomatosis, which is often associated with common variable immunodeficiency. Abnormal calcium metabolism was recognized in sarcoidosis more than 60 years ago, and despite being observed only in 10% of patients, it may be helpful to consider sarcoidosis in some settings.

The ESR is frequently elevated but is not useful in assessing disease activity. CRP is mildly elevated in about one-third of sarcoidosis patients but does not differentiate sarcoidosis from other causes of inflammation. The results show only a variable correlation with fatigue among sarcoidosis patients. The relationship between CRP and response to therapy is under investigation.

Serologic markers, such as serum ACE, adenosine deaminase (ADA), serum amyloid A (SAA), and soluble interleukin-2 receptor (sIL2R), have been examined for potential roles in diagnosis or monitoring disease activity. The ACE level is elevated in 75% of untreated sarcoidosis patients. However, serum ACE has limited utility as a diagnostic test due to poor sensitivity and insufficient specificity (an almost 10% rate of false positive results). Although several studies showed a correlation between serum ACE level and abdominal involvement of the disease, the value of monitoring ACE levels to assess the course of the disease remains unclear. Elevated ADA levels may be found in serum and bronchoalveolar lavage fluid in sarcoidosis patients. SAA also increased in sarcoidosis. However, given the low sensitivity and specificity of these tests, the clinical use...

**Table 1. Sarcoidosis: organ involvement percentage, common morbidities and symptoms**

<table>
<thead>
<tr>
<th>Organ involvement*</th>
<th>Percent**</th>
<th>Morbidities and symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lungs</td>
<td>95</td>
<td>Dyspnea, cough, chest pain, decreased pulmonary function (restrictive or obstructive), pulmonary fibrosis, pulmonary hypertension, pulmonary embolism, intermittent flare/exacerbations</td>
</tr>
<tr>
<td>Skin</td>
<td>15</td>
<td>Lupus pernio, maculopapular rash, nodules, plaques, alopecia, hypo/hyperpigmentation, scales, annular lesions</td>
</tr>
<tr>
<td>Non-thoracic lymph nodes</td>
<td>15</td>
<td>Discrete, movable, non-tender lymph nodes</td>
</tr>
<tr>
<td>Eye</td>
<td>12</td>
<td>Uveitis, lacrimal gland enlargement, peri orbital swelling, keratoconjunctivitis sicca, optic neuroophathy (potentially leading to blindness), conjunctival nodules and follicles, dacryocystitis, retinal vasculitis</td>
</tr>
<tr>
<td>Liver</td>
<td>11</td>
<td>Cholestatic or obstructive liver disease, cirrhosis, portal hypertension, abdominal pain, liver function abnormalities.</td>
</tr>
<tr>
<td>Erythema nodosum</td>
<td>8</td>
<td>Lofgren's syndrome (erythema nodosum, uveitis, lymphadenopathy)</td>
</tr>
<tr>
<td>Spleen</td>
<td>7</td>
<td>Abdominal pain/pressure or hematological abnormalities</td>
</tr>
<tr>
<td>Neurologic</td>
<td>5</td>
<td>Cranial nerve abnormalities or palsy, seizures, meningitis, peripheral neuropathy, pain, neuropsychiatric symptoms, endocrine abnormalities from pituitary or hypothalamic involvement</td>
</tr>
<tr>
<td>Constitutional</td>
<td>80</td>
<td>FEVERS, fatigue, weight loss, night sweats, malaise</td>
</tr>
</tbody>
</table>

*Only the most common organ involvement is presented.

**Percent of patients with organ involvement at presentation with sarcoidosis from the ACCESS study (n=736 sarcoidosis patients)
of both markers is also limited. Interestingly, serum sIL2R has been suggested as a useful marker to determine extrapulmonary involvement in sarcoidosis patients [9].

Our patient's initial blood test showed slight lymphopenia, hypergammaglobulinemia, and elevated CRP and ESR. Further tests revealed high ACE levels.

**IMAGING**

Conventional chest radiography still provides crucial information for the diagnosis of sarcoidosis. Identification of the lung and lymph node involvement is the basis of the Scadding classification: normal (stage 0), BHL (stage 1), BHL accompanied by pulmonary infiltrates (stage 2), pulmonary infiltrates without BHL (stage 3), and overt pulmonary fibrosis (stage 4). When lymph nodes are seen, both right and left hilar lymph nodes are most frequent (95% each). The lung parenchymal findings are more varied and include normal, diffuse reticular or ground glass opacities, nodular consolidation, and cystic scarring.

High-resolution CT of the chest is indicated in cases of atypical clinical or radiographic findings, clinical suspicion of the disease despite normal chest radiography and complications (especially for stage 4), airflow limitation, or pulmonary hypertension [10].

In our case, the patient's primary complaint was abdominal pain, and only further questioning alerted us to her chronic cough and fatigue. Later, the findings on her abdominal and chest CT scans prompted the need for a bronchoscopy and tissue for biopsy.

**BRONCHOSCOPY AND BRONCHOALVEOLAR LAVAGE**

Several diagnostic modalities may be achieved through bronchial flexible endoscopy: macroscopic examination of airways, endobronchial biopsy (EBB), transbronchial lung biopsy (TBB), transbronchial needle aspiration (TBNA), and bronchoalveolar lavage.

Macroscopically, bronchial mucosa may be normal or may reveal various abnormalities. The classic endobronchial sarcoidosis is well documented, characterized by waxy yellow mucosal nodules 2–4 mm more profuse in the lobar and the segmental bronchi. Coalescence of the nodules may obscure the bronchial lumen mimicking a malignant mass. The sensitivity of EBB is lower than that of TBB. Adding EBB to TBB is beneficial, significantly improving its diagnostic performance. In recent years, needle aspiration of intrathoracic lymph nodes has attracted much interest for sarcoidosis diagnosis. TBNA might become an alternative to starting with EBB and TBB in patients with stage 1 or stage 2 sarcoidosis. Bronchoalveolar lavage is a safe minimally invasive procedure which originally identified the T1 helper-related lymphocytic and macrophagic alveolitis in sarcoidosis. The characteristic finding is a moderate (20–50%) lymphocytosis in 80% of cases and a T lymphocyte CD4/CD8 ratio > 3.5 in 50% of cases showing a specificity of 93–96% [10].

No macroscopic abnormalities were observed in the upper airways of our patient. Bronchoalveolar lavage demonstrated high levels of CD4 and CD4/CD8 ratio. Biopsies were taken and the pathology report described non-caseating granulomas in the interstitium, consisting of epithelioid histiocytes and multinucleated giant cells wrapped by hyaline fibrosis.

As expected, the pathology report combined with bronchoalveolar lavage results, imaging, and clinical manifestations confirmed the diagnosis of sarcoidosis.

**TREATMENT**

In general, sarcoidosis treatment should be offered to palliate symptoms and improve quality of life or to prevent end-organ disease. Initial therapy is usually prednisone or a similar glucocorticoid. The optimal initial dose, timing of dose reduction, maintenance dose, and decision to stop treatment are based on clinical experience, given that no formal data are available for guidance. Since many patients are intolerant to prednisone, steroid-sparing alternatives have been studied. Methotrexate is the most widely used antimetabolite, but azathioprine, leflunomide, and mycophenolate have also been helpful. The biologic agents, especially monoclonal anti-tumor necrosis factor (anti-TNF) antibodies, have been shown to be effective in patients after other treatments failed. Infliximab, the most widely studied anti-TNF antibody, has been shown to be effective for refractory sarcoidosis (range implies more than one. For the clinician, treatment options enable to use a specific treatment regime for each patient, which minimizes risk while enhancing benefit [11].

Due to our patient's young age and knowing the harmful effects of long-term steroid use, we decided to start treatment with 40 mg prednisone every 2 days with a goal to taper down.

At the 3-month follow-up, the patient's condition had ameliorated and she felt well. Her abdominal pain subsided and she remained asymptomatic taking 20 mg prednisone every 2 day. At the 6-month follow-up, she reported playing volleyball with her neighborhood team three times per week with no respiratory problems and taking 20 mg prednisone every 2 days without mentioning any side effect connected to the treatment.

**CONCLUSIONS**

This clinical education case, which ultimately demonstrates the complex nature of most internal medicine cases, shows the difficulty in making clinical decisions and further promotes reaching a diagnosis after excluding the myriad number of diseases that sarcoidosis, a systemic inflammatory disease, may imitate.

**Correct answers**

1. e
2. b
3. c
4. c
Correspondence
Dr. E. Galron
Dept. of Internal Medicine D, Barzilai Medical Center, Ashkelon 78346, Israel
Fax: (972-8) 674-5591
email: udigalron1@gmail.com

References

Capsule
Targeting cardiomyocyte cell death
Narrowing of blood vessels, arrhythmias, and congenital heart defects are all signs of heart disease. Because of the high prevalence of these conditions, developing treatments to minimize death of heart muscle cells (cardiomyocytes) is needed. To understand cardiovascular disease, Fieder et al. used human stem cell-derived cardiomyocytes and mouse models. They noticed an increase in a protein kinase called MAP4K4 in defective heart tissue. Lack of oxygen induces MAP4K4 to signal cell death. Cardiomyocyte viability and function can be rescued by blocking MAP4K4 with the small-molecule inhibitor DMX-5804, and in mice, infarct size is reduced within an hour of MAP4K4 inhibition.

Capsule
A pharmacological hat trick
The number of people with type 2 diabetes (T2D) may reach 510 million by the year 2030, a trend largely driven by the global rise in obesity rates. Because T2D often compromises kidney function, the number of people with kidney failure is also expected to rise dramatically. A new study suggests that a drug already in clinical use for T2D may provide multiple health benefits to such patients. Canagliflozin lowers blood glucose levels by blocking reabsorption of glucose in the kidney. In a large randomized trial of patients with T2D and chronic kidney disease, Perkovic and colleagues found that those receiving canagliflozin were 30% less likely to develop end-stage kidney disease and 20 to 30% less likely to develop cardiovascular disease than those receiving placebo.

Capsule
Recall responses by human natural killer cells
One of the traditional dividing lines separating innate and adaptive immunity is the restriction of immune memory to adaptive immune cells. However, accumulating evidence in animal models has suggested that memory responses can be evoked in natural killer (NK) cells. Nikzad et al. evaluated whether human NK cells also exhibit memory responses. They analyzed NK cells recovered from humanized mice and NK cells found in the viral antigen-challenged skin of adult volunteers who had chickenpox as children. Antigen-specific recall responses by human NK cells were observed in both experimental systems. Thus, human NK memory responses contribute to host protection after vaccinations or natural infections.