Published in final edited form as:

Pediatr Rev. 2020 October ; 41(Suppl 1): S94–S97. doi:10.1542/pir.2018-0312.

Fever and an Abdominal Mass in an 18-month-old Boy

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Presentation

An 18 month-old boy from Saudi Arabia presents with four months of vomiting, diarrhea, poor weight gain and daily fevers. He also had a long-standing history of lymphadenopathy as well as an abdominal mass, for which evaluation and management had consisted of a non-diagnostic biopsy of the abdominal mass and multiple courses of empiric antibiotic and antifungal medications for a presumed infectious etiology. He continued to have daily fevers and a persistent mass so the family came to the United States of America (USA) for further evaluation.

His past medical history is notable for birth at 31 weeks gestational age via Cesarean section due to maternal hypertension and subsequent hospitalization for one month without sequelae of prematurity. His immunizations are up to date according to the Saudi Arabia immunization schedule, including the oral polio and the Bacillus Calmette-Guérin (BCG) immunizations.¹ He developed a fever at two months of age for three days followed by the development of unilateral axillary lymphadenopathy, which never resolved and was persistent on presentation. The family history is notable for his parents being first cousins. They had had difficulty conceiving and experienced multiple miscarriages prior to the patient's birth. He has no sick contacts, no animal exposures, and has not consumed unpasteurized foods.

On presentation, the patient has a temperature of 38.3 degrees Celsius and heart rate of 140 beats per minute. He is 9.9kg (30% corrected for gestational age), 76.2cm (7% corrected for gestational age), and 58% weight for length according to WHO growth standard. On physical exam, he is slim-appearing with abdominal distention, has abdominal tenderness, and has a left-sided axillary lymph node that is approximately 2.5 cm in diameter, mobile, firm, and non-tender. The initial laboratory evaluation (Table 1), is notable for leukocytosis, microcytic anemia, and elevated inflammatory markers. Blood culture, tuberculin skin test, and QuantiFERON-TB Gold™ are negative. Quantitative immunoglobulins show slightly

elevated IgA level and low IgM level. T-cell subsets show a low absolute CD4+ lymphocyte count.

Differential Diagnosis

The differential in this situation includes infectious etiologies endemic to Saudi Arabia such as basidiobolomycosis or visceral leishmaniasis, bartonellosis, tuberculosis, non-tuberculosis Mycobacterial infection, HIV, antibiotic-resistant salmonellosis, and other opportunistic infections. Additional considerations include malignancy and immune deficiencies.

Diagnosis

A computed tomography (CT) scan showed a 5cm intraperitoneal mesenteric mass (Figure 1, panel A). He underwent laparoscopic biopsy of the mass. The pathology showed the mass was composed of lymphoid tissue, fibrosis, chronic inflammation, scattered giant cells and abundant acid-fast bacilli. Tissue culture grew *Mycobacteria tuberculosis* complex after seven days. *M. tuberculosis* complex can include both *M. tuberculosis* and *M. bovis*. Given the patient's history of BCG vaccination, and absence of *M. tuberculosis* risk factors, there was concern for a disseminated infection with *M. bovis* from BCG vaccination and for an underlying primary immunodeficiency. Genotyping of the organism confirmed a Mycobacterial interspersed repetitive-unit pattern consistent with a *M. bovis* BCG strain. The patient was diagnosed with a disseminated infection with *M. bovis* BCG strain in the setting of a likely primary immunodeficiency.

Complications of BCG Vaccination

Although not part of the standard vaccination schedule in the USA, live-attenuated BCG immunization is administered at birth worldwide in areas with endemic *M. tuberculosis*. BCG vaccine complications are uncommon due to the low virulence of the organism but include local reactions, lymphadenopathy and disseminated infection.² The infections may be more severe in patients with underlying immune deficiencies.²

Post-vaccination lymphadenitis can present with unilateral non-tender lymphadenopathy developing two to four months after vaccination.² After the introduction the BCG SSI Danish strain 1331 in 2005, there was an increase in the incidence of vaccine-related lymphadenitis in Saudi Arabia.³ Notably, our patient presented after 2005. Depending on the symptoms and duration, management approaches may include observation, aspiration, or surgical excision.² For more concerning presentations such as disseminated lymphadenopathy, anti-mycobacterial treatment is recommended.² Severe, post-vaccination infections due to *M. bovis* BCG strain are typically only seen in patients who have acquired or inherited immune deficiencies.^{4,5} However, the BCG vaccine is commonly administered after birth before immunodeficiencies are recognized.⁶ In patients with disseminated lymphadenopathy after vaccination, it is important to consider a primary immunodeficiency such as severe combined immunodeficiency, chronic granulomatous disease, Mendelian

Susceptibility to mycobacterial disease (MSMD), HIV, DiGeorge Syndrome, or Hyper IgM and IgE syndromes.^{4–6}

IFN- γ /IL-12 Pathway and Immunodeficiencies Associated with Mycobacterial Infection

The immune system typically eliminates mycobacteria using the IFN- γ /IL-12 pathway, in which T-cells signal to macrophages to destroy phagocytosed mycobacteria.^{7,8} Single defects in this pathway that affect the immune system's ability to eliminate mycobacteria have been identified.⁴ Mutations in both autosomal and X-linked genes have been shown to cause MSMD. Multiple genes have been identified as causative including defects in the cytokine, cytokine receptor, or the signaling pathways for IFN- γ , IL-12 and IL-23.^{4,5,7,8} Nonetheless, half of patients with disseminated BCG-strain *M. bovis* infection may not have an identifiable mutation.⁸

Further evaluation of our patient revealed undetectable interleukin-12 (IL-12) and interferon-gamma (IFN- γ) levels. Genetic testing with a single nucleotide polymorphism microarray was normal except for areas of homozygosity, consistent with a history of consanguinity. Further testing with whole exome sequencing did not reveal any known mutations in the IFN- γ /IL-12 pathway or genes associated with human disease. Therefore, it was suspected the patient had an intronic mutation (a non protein-coding mutation) in the IFN- γ /IL-12 pathway. The patient also had a low CD4 count. Since T-cells are responsible for IFN- γ production, this could also have contributed to the undetectable level of IFN- γ . His T-cell subsets could not be repeated before departure, so it remains unknown if the low CD4 count was transient or reflective of a more global T-cell problem. However, there was low suspicion that the low IFN- γ was caused primarily by a T-cell defect because the patient had never developed opportunistic infections (e.g. *Candida* or *Pneumocystis*) that can be seen with T-cell defects.

BCG infections due to primary immunodeficiency most commonly present among pediatric patients. In a case series from China, seventy-four cases were identified from 2007 – 2012 as developing local or disseminated lymphadenopathy after receiving the BCG vaccine within two days of life. Thirty-two of the children (43%) had a definitive primary immune deficiency, of which four had low IFN- γ production.⁹ At follow-up, two children were cured after receiving two years of anti-tuberculosis therapy, one died, and one was still undergoing treatment.⁹ In a case series of disseminated BCG after vaccination in twelve Saudi children, all had an underlying primary immunodeficiency, received treatment with anti-tuberculosis therapy, and all but one had a favorable response.¹⁰

Treatment and Clinical Course

Our patient was initially treated with isoniazid, pyranizamide, ethambutol, and rifampin. When antibiotic susceptibilities revealed mono-resistance to pyrazinamide, a hallmark of *M. bovis*, pyrazinamide was discontinued. Ethambutol was later discontinued due to an acute kidney injury.

Four weeks after starting anti-mycobacterial therapy, he developed a severe flare of intestinal inflammation leading to small bowel obstruction, intestinal perforation requiring surgical repair and became critically ill. Given the timing and absence of alternative explanation of this acute worsening inflammation after initiation of anti-mycobacterial treatment, we felt this presentation was consistent with a paradoxical reaction. Such worsening of symptoms developing after initiation of tuberculosis treatment have been described in pediatric and adult patients both with and without HIV.^{11,12} In children, described risk factors include those with weight below the 25th percentile and with disseminated disease.¹³ Though this phenomenon has been noted in children after initiating tuberculosis treatment,¹² it has not been commonly described in the setting of a BCG infection.

In certain patients, such as those undergoing antiretroviral therapy, glucocorticoids have been used for treatment of paradoxical reaction or tuberculosis-associated immune reconstitution syndrome. Steroid treatment has been shown to reduce hospitalizations and need for therapeutic procedures; however, this treatment is not well studied.¹⁴ After deliberation, this patient was not treated with steroids due to concern it may inhibit wound healing. Once he stabilized, he began treatment with subcutaneous IFN- γ , which was discontinued after three months owing to lapse in medical insurance coverage. After nine months from presentation, the patient was thriving and a repeat abdominal CT scan revealed complete resolution of the abdominal mass (Figure 1, panel B).

There are limited studies regarding treatment of infection due to *M. bovis* and those with underlying immunodeficiency. As *M. bovis* is intrinsically resistant to pyrazinamide, treatment has been extrapolated from pyrazinamide - resistant *M. tuberculosis* and consists of isoniazid, rifampin and ethambutol for the initial two months followed by isoniazid and rifampin for seven additional months.¹⁵ Some case reviews suggest addition of IFN- γ to anti-mycobacterial treatment may improve survival if patients have a MSMD.^{9,16} However, the definitive cure of the underlying immune defect is hematopoietic stem cell transplant.

Ultimately, our patient was treated with standard anti-mycobacterial therapy for nine months and three months of replacement IFN- γ . Despite a significant complication of suspected paradoxical reaction leading to abdominal perforation, he had resolution of the infection as demonstrated by a full clinical recovery and resolution of the mass. At this point, he returned to his home country and was advised to continue isoniazid and rifampin until follow-up was established.

Author Disclosure:

Dr. Kochis receives support from NIH training grant T32: 5T32HD044355-15. Dr. Lederman reports a grant and consulting for EryDel, unrelated to the content of this article. Dr. Milstone reports consulting for BD, unrelated to the content of this article. Dr. Jain reports consulting for Mediso, unrelated to the content of this article. Dr. Sick-Samuels receives support from NIH training grant T32 A1052071. Dr. Troch has no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

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Lessons for the Clinician

- In children from regions with endemic *M. tuberculosis* with routine BCG vaccination, lymphadenopathy may be a presenting symptom of local or disseminated disease from BCG infection.²
- Immunodeficiencies should be on the differential for all patients with disseminated lymphadenopathy.^{3,5,6}
- The immune system eliminates mycobacteria using the IFN- γ /IL-12 pathway, in which the T-cells signal to macrophages to destroy the phagocytosed mycobacteria.^{7,8}
- Paradoxical reaction or worsening of presenting symptoms can occur after initiation of anti-tuberculosis treatment.^{11–14}
- The use of first line anti-tuberculosis therapy and exogenous IFN- γ may be an effective treatment regimen for children with disseminated BCG and an underlying IFN- γ pathway defect.

Figure 1.

Panel A. Abdominal CT scan showing 5.4 cm solid intraperitoneal mesenteric mass. Panel

B. Follow-up abdominal CT scan at 9 months showing resolution of the mass.

Key: * - Mass, L-Liver, Sp-Spleen, St - Stomach, B - Bladder, I - Intestines

Table 1.

Initial Laboratory Test Results

Laboratory Test		Result	Reference Ranges
CBC with Differential	WBC	15.2 k/cu MM	6–17.5 k/cu mm
	Neutrophils	58%	25–49%
	Immature Granulocytes	1.4%	0–1%
	Lymphocytes	21.1%	40–76%
	Monocytes	13.6%	2–7%
	Eosinophils	5.1%	1–4%
	Hemoglobin	9.1 g/dL	11.6–13.6 g/dL
	MCV	62.7 fL	70–86 fL
Inflammatory Markers	ESR	24 mm/hr	1–15 mm/hr
	CRP	4.8 mg/dL	< 0.5 mg/dL
CMP	AST	52 U/L	0–37 U/L
Quantitative Immunoglobins	IgG	674 mg/dL	330–1165 mg/dL
	IgA	138 mg/dL	15–105 mg/dL
	IgM	27 mg/dL	40–160 mg/dL
T-Cell Subsets	Absolute CD4+	231/cu mm	1300 – 3400/ cu mm
Microbiology	Blood Culture	Negative	
	HIV Serologies	Negative	
	Tuberculin Skin Test	0 mm of induration	
	QuantiFERON-TB Gold™	Negative	