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A 2-year-old boy presented to his primary care provider with a 2-week history of daily fevers (to 39°C), malaise, increasing pallor, decreased appetite, and a 3-lb weight loss. Review of systems was otherwise negative (no history of cough, vomiting, diarrhea, or rash). The child was fully immunized and had no relevant past medical problems. His first cousin had been treated for autoimmune hemolytic anemia (AIHA) 3 years prior. An office-based complete blood count found leukocytosis (39 000 cells/ μ L) and profound anemia (hemoglobin 6.3 g/dL); platelets were read as “clumped” and therefore were uninterpretable. A presumptive diagnosis of acute leukemia was entertained, and the child was transferred to our institution for further management.

The child was well developed and in no distress. Height and weight plotted at the 95th and 25th percentiles, respectively. Temperature was 37.2°C, heart rate was 176 beats per minute, and regular and blood pressure, initially obtained at 148/99 mm Hg in the first minutes of hospitalization, later normalized. Respirations were regular and unlabored at 38 per minute, and resting oxygen saturation was 93% as measured by pulse oximetry. HEENT examination was unremarkable and there was no evidence of exanthem, purpurae, or abnormal lymphadenopathy. There was tachycardia without murmur. Auscultation of the chest revealed the presence of breath sounds on both sides and no rales or rhonchi. Only when auscultatory findings were directly compared from one side to the other were decreased breath sounds on the left side appreciated. The abdomen was soft and there was no hepatosplenomegaly. Neurologic examination, including gait, was normal for age.

A complete blood count confirmed a leukocytosis (40 100 cells/ μ L), but the differential was inconsistent with acute leukemia; there were only 1% blasts. Rather, neutrophils and bands together accounted for 80% of total white cells. In addition, there were 14% lymphocytes, 3% plasma cells, and 2% nucleated red blood cells. Hemoglobin was 5.1 g/dL, hematocrit 14.8%, and platelet count 657 000/ μ L. The mean corpuscular volume

was 96 fL, and the reticulocyte count was 6.4%. The peripheral blood smear revealed thrombocytosis, a left-shifted leukocytosis including scattered early myeloid forms and blasts, moderate erythrocyte polychromasia, anisocytosis, and slight macrocytosis (Figure 1). Serum electrolytes and uric acid were essentially normal, but lactate dehydrogenase was elevated at 423 U/L. Flow cytometric analysis of the peripheral blood, performed to investigate the possibility of a clonal process such as leukemia, revealed a polyclonal, reactive leukocytosis of normal blood cells. We interpreted the elevated reticulocyte count to be consistent with a destructive red cell process and investigated various causes of hemolysis. A direct Coomb’s test was strongly positive for both IgG and deposition of C3 complement. We next considered the child’s tachypnea, hypoxia, and differential breath sounds. The chest radiograph was markedly abnormal, showing near-complete opacification of the left hemithorax (Figure 2A). To differentiate a primary pneumonic process from a pleural accumulation, a chest computed tomography scan was performed (Figure 2B). The computed tomography scan found evidence of a large left pleural effusion with almost complete collapse of the underlying lung and a slight rightward mediastinal shift. A blood culture rapidly grew gram positive cocci in pairs and chains, later identified as *Streptococcus pneumoniae*. The child was thus diagnosed with AIHA associated with pneumococcal pneumonia, empyema, and bacteremia. He was transfused with red blood cells and treated with a combination of ceftriaxone and vancomycin. The next day, video-assisted thoracoscopic surgery (VATS) with decortication was performed to remove infectious material surrounding the left lung. A moderate amount of thick fluid within the left chest

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Figure 1. Peripheral blood smear findings on presentation. Thrombocytosis (abundant platelets) and a left-shifted leukocytosis (elevated white blood cell count) are apparent with many neutrophils and band forms present, as well as scattered early myeloid forms (black triangle) and plasmacytoid lymphocytes (white triangle). Examination of the erythroid lineage reveals abundant polychromasia (differences in cell color), a moderate degree of poikilocytosis (variation in cell shape), anisocytosis (variation in cell size), and the occasional nucleated red blood cell (black arrow). Together, this peripheral blood smear is consistent with inflammation/infection coupled with a destructive red cell process and a robust compensatory erythroid marrow response. This smear is not typical for acute leukemia because of the high platelet count, robust erythropoietic response, and absence of early blast forms. Magnification 200 $\times$ (A-C) and 630 $\times$ (D-F)

along with a substantial rind of fibrinous debris lining the lung was removed. A gram stain of the pleural peel revealed the presence of gram-positive cocci, and a culture of the pleural fluid grew out *S pneumoniae*. The child tolerated the surgical procedure well, and his tachypnea, hypoxia, and fever promptly resolved after VATS. A follow-up chest radiograph confirmed re-aeration of the left lung (Figure 2C).

The patient was treated with intravenous vancomycin and ceftriaxone over the next several days. Interestingly, the autoimmune hemolytic process seemed to respond to transfusion and treatment of the pneumococcal infection. The patient required packed red blood cells (20 mL/kg total) but was not treated with high-dose glucocorticoids. Our rationale for initially withholding steroids was to maximize the immune response to the pneumococcal infection, but it soon became apparent that the patient's red cell levels had stabilized simply by transfusion and management of the pneumococcal infection. The child's hemoglobin rose to 7.9 g/dL

following transfusion and progressively increased without further transfusion until a discharge level of 9.1 g/dL. The child was prescribed a 14-day outpatient course of oral levofloxacin and recovered fully within the next several days. He has had no recurrence of AIHA, and a follow-up chest radiograph 2 months after hospitalization showed near total resolution of the left pneumonia and empyema (Figure 2D).

Discussion

We present the unusual case of a 2-year-old child whose presentation (fevers, weight loss, leukocytosis, and anemia) initially seemed most consistent with acute leukemia. Indeed, in most cases, this history along with a high white blood cell count and striking anemia would certainly be caused by acute leukemia. Instead, this child had 2 separate concurrent medical problems—a severe pneumococcal infection and AIHA. Occurring in roughly 1 in 80 000 children with a peak incidence below 4 years of

Figure 2. Chest radiographs (A, C, D) and representative chest computed tomography image (B) of the patient at presentation (A, B), after chest tube placement and drainage of copious pleural fluid (C), and then 2 months after hospitalization (D). Note the almost complete “white-out” of the left lung on presentation (A, B), re-expansion of the left lung after VATS procedure and insertion of chest tube (C), and near-complete resolution 2 months later (D)

age, AIHA is caused by a misdirected humoral response against 1 or more surface antigens on red blood cells.¹ Many cases seem to follow common viral infections of childhood.² Though we cannot conclusively demonstrate that the trigger for this child's AIHA was the concurrent pneumococcal infection, it is curious that the child's hemolytic process seemed to respond to therapy directed at the underlying pneumococcal infection. We were surprised by this since this child's AIHA was mediated by IgG whose serum half-life is roughly 3 weeks³ and no immunomodulatory treatments (such as glucocorticoids, plasmapheresis, or IVIg)⁴ were administered. The

hemoglobin stabilized by red cell transfusion and increased daily thereafter. We hypothesize that the plasma cell responsible for the anti-red cell antibody may have been triggered by the active pneumococcal infection and that effective clearance of bacteria through a combination of antibiotic and surgical approaches coincidentally diminished the activating signals that stimulated the plasma cell to make the errant antibody. We speculate that the reason why the hemolysis resolved so quickly may be because the anti-erythrocyte antibody may have been of low titer or perhaps because the transfused red cells lacked the antigen to which the antibody was directed.

There are several published reports of anemias concurrent with infectious processes. Septic shock and disseminated intravascular coagulation from any number of infectious causes, for example, are commonly associated with anemia, most likely through a combination of inflammatory-mediated inhibition of hematopoiesis and microangiopathic peripheral destruction of erythrocytes as evidenced by schistocytes on the peripheral blood smear. Considering *Pneumococcus* in particular, most published reports of concomitant anemias have been associated with pneumococcal-mediated hemolytic uremic syndrome.^{5,6} With respect to AIHA, we found only 1 published report linking pneumococcal infection and autoimmune hemolysis, but this case described AIHA associated with severe *S pneumonia* sepsis and bacteremia rather than pneumonia.⁷ To our knowledge, our patient represents the first published report of AIHA in association with a severe pneumococcal pulmonary infection. There are reports of other organisms being able to cause AIHA, in particular, *Mycoplasma pneumoniae*⁸ and viral infections such as cytomegalovirus⁹ and Epstein–Barr virus.¹⁰ Though AIHA and underlying viral, bacterial, or atypical infections have been documented, the pathophysiologic mechanisms linking them are likely complex and multifactorial. Our patient's case suggests that, beside transfusion support, effectively treating a documented bacterial infection in patients with autoimmune hemolysis may be sufficient medical management for AIHA in some cases.

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