**CLINICAL CASE**:  My baby has a high fever and a bad cough

Lee, a six-month-old infant, is brought to the pediatric emergency room (ER) by his mother at about 8 AM on a Saturday. She tells you that Lee was well until two days ago, when he developed a cough and seems lethargic. At that time, she called her family physician. He advised her that it was probably a cold, to keep him well hydrated, and to administer one baby acetaminophen every 6 h if Lee develops a fever.

Lee slept poorly that night and the next day was noted to have a low-grade fever of about 38°C. Since he seemed to be getting worse, the family physician was called again, but he continued to think Lee merely had a cold and should be treated symptomatically. Over the course of the day Lee's cough became more frequent, and by the evening he was breathing more rapidly than usual (tachypneic). These symptoms became more intense during the night and prompted the mother's visit to the ER with the baby.

Your physical examination of Lee discloses a child of appropriate length and weight (normal growth) who has a normal overall appearance, that is, no dysmorphic facial features or bone abnormalities. He has an elevated temperature of 38.5°C and obvious respiratory symptoms (coughing and rapid breathing) but no meningeal signs such as neck rigidity or inconsolable irritability.

Auscultation of his chest reveals coarse breath sounds but no bronchospasm or evidence of pulmonary consolidation. Examination of the pharynx reveals no evidence of pharyngitis or tonsillitis (inflammation of the phyarynx and tonsils); in fact, *the tonsils seem reduced in size*.

You surmise that the patient has a pulmonary infection (probably a bacterial pneumonia) and have him admitted to the pediatric ICU (PICU). You also order a chest X ray, blood cultures, and a complete blood count (CBC).

The chest X-ray result is available shortly after admission to the PICU (Pediatric ICU) and reveals the presence of bilateral perihilar infiltration. A complete blood count shows an *increased white blood cell* (WBC) count (15,500 cells/µL, reference range < 12,000 cells/µL) *comprising 72% neutrophils, 7% monocytes, and 20% lymphocytes*. Although this differential is compatible with the presence of an infection, *you note* that the total white count is lower than you expected for bacterial pneumonia.

In any case, you start the patient on IV cefotaxime, a broad-spectrum third-generation cephalosporine antibiotic to treat what you consider is the likely cause of his pneumonia, a bacterial pathogen.

You also order a lung computer-aided tomography (CAT) scan to obtain an objective baseline for the extent of the infection.

Over the next several days you return frequently to the PICU to check on Lee's condition. Over this period Lee's respiratory status remains stable but does not improve despite the antibiotic therapy. He continues to be febrile and to be tachypneic. Pulse oximeter readings show periodic episodes of oxygen desaturation (< 92%) that require treatment with an oxygen mask.

The blood cultures have proved negative, so you know neither the identity of the organism nor its sensitivity to antibiotics. Thus, you cannot be sure his infection is being adequately treated and, in fact, his lack of more rapid clinical improvement suggests otherwise.

On the morning of the fourth day after admission, Lee's status seems to have deteriorated; his breathing is more labored and oxygen desaturation episodes are more prolonged and frequent. Indeed, a repeat CAT scan shows more extensive lung involvement.

After consultation with a pulmonologist, a bronchoscopy is performed to obtain bronchial lavage fluid and brushings for microscopic examination and culture. This is done without incident. The next morning the laboratory report is returned; to your surprise, Lee has an infection with *Pneumocystis jiroveci* (formerly called *Pneumocystis carinii*) a protozoal organism that ordinarily causes infection only in immunocompromised hosts. You immediately change the antibiotic to IV trimethoprim-sulfamethoxazole (Bactrim), a specific and effective therapy for this organism.

The results of this treatment are dramatic. Within 24 h Lee shows noticeable improvement. Over the next several days he defervesces and his pulmonary status returns to normal. After four days of IV Bactrim therapy you switch to oral therapy and two days later Lee is discharged to home with the proviso that he continue on oral Bactrim therapy for another two weeks. Pneumocystis belongs to a category of organisms known as opportunistic pathogens, because they do not cause disease in healthy individuals, but do so in immunocompromised individuals.

Recognizing that Lee may have an immunologic disorder, you refer him to an immunologist for further workup. The immunologist starts the workup with a second look at the facts already in hand.

First, the history of normal development and lack of disease during Lee's first six months of life speak against SCID, an immunodeficiency that generally declares itself early and is associated with a failure to thrive. This tentative conclusion is corroborated by the CBC, which did not show the presence of lymphopenia (reduced lymphocyte count).

 It should be noted, however, that Lee was observed to have a reduced tonsillar mass, possibly indicating some loss of ability to populate peripheral lymphoid compartments.

Re-review of the chest X-ray and CAT scans confirms the presence of a thymic shadow, with a size appropriate for age. Combined with the lack of evidence of hypoparathyroidism, dysmorphic facial features, and cardiac anomalies, the presence of a thymic shadow on radiologic examination eliminates consideration of thymic aplasia (DiGeorge syndrome).

HIV diagnostic test performed on Lee's mother during childbirth (as required by your state's law) was negative. Nevertheless, to be absolutely certain, Lee is tested for the presence of HIV using a Western blot-based technique to detect HIV protein, in case he lacks the ability to mount an antibody response to this organism. The results of this test are likewise negative, and HIV infection is definitively ruled out.  
  
The immunologist also elicits a family history from the mother. He learns that Lee has a maternal uncle (his mother's brother) who died mysteriously at an early age due to pneumonia. This suggests that Lee may have an X-linked disease.

Extensive workup is therefore initiated. Although the *Pneumocystis* infection is drawing attention to the T cells or cell-mediated arm of the immune response, the status of his humoral immunity is also investigated.

Quantitation of peripheral lymphoid subsets by an initial flow cytometry study reveal normal percentages and absolute numbers of CD4+ T cells, CD8+ T cells, B cells, and natural killer (NK) cells. Additional studies are performed in a specialty laboratory that does a more extensive panel of CD markers.

Analysis of the CD4+ cell subsets reveals that the percentage of CD4+ cells in the CD4+/CD45RA+ (naive) CD4 T-cell subset is high and, correspondingly, the percentage in the CD4+/CD45RO+ (mature) CD4 T-cell subset is low even if one considers the fact that the ratio of CD45RA+ cells to CD45RO+ cells is high in young children as compared to adults. In addition, while Lee has a normal number of B cells, virtually none bear surface IgG or IgA.

**Immunoglobulin Levels**:

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| --- | --- | --- |
|  | **Results** | **Reference Range** |
| IgM | 407 mg/dL | 65 ± 25 mg/dL |
| IgG | < 50 mg/dL | 923 ± 256 mg/dL |
| IgA | < 5 mg/dL | 124±45 mg/dL |

In cell cultures Lee's T cells, stimulated by anti-CD3/anti-CD28, fail to induce normal B cells to produce IgG or IgA,   One type of immunodeficiency that fits this pattern is hyper-IgM syndrome, an immunodeficiency that may be caused by failure to express CD40L (CD154) on the surface of activated T cells.

At this point the immunologist closes in on the diagnosis of X-linked hyper-IgM syndrome (XHIGM; HIGM-I) by performing flow cytometry studies using fluorochrome-labeled anti-CD40L.  The immunologist also sends a sample of Lee's DNA to a sequencing facility for sequencing of the CD40L gene. The results show that Lee's CD40L gene has a mutation in the extracellular domain of the gene that results in a truncation of this domain and thus low expression of CD40L on the T-cell surface.  Given the family history of a maternal uncle with an illness that could have been caused by HIGM, Lee is assumed to have inherited this mutated X-linked gene rather than to have a new mutation. This was subsequently verified by sequencing of Lee's mother's DNA, which showed that the mother carries the mutated gene on one X chromosome.

Lee is placed on monthly intravenous immunoglobulin (IVIG) infusions of 20 mg/kg to bring his "trough" (low-point) IgG level above 500 mg/dL, the target IgG level for immunodeficiency patients who cannot produce normal amounts of IgG. In addition, he is placed on prophylactic Bactrim therapy to prevent recurrence of *Pneumocystis* infection.

1. How do the results obtained thus far differ from what would be found in studies of patients with XLA, SCID, and Common Variable Immunodeficiency OR Common Variable Immunoglobulin deficiency (CVID)??

2.Does The data  offer functional evidence that Lee's T cells are functionally deficient either because they do not express CD40L or because they express an inactive CD40L??

3.What is the explanation for the initial observations  that Lee's tonsils are underdeveloped and that his peripheral helper T cells are skewed toward the naive (CD45RA) subset rather than the memory (CD45RO) subset??