Jackson Smith was born relatively healthy after an uneventful pregnancy. His parents are both in good health and he has three healthy older siblings. Soon after delivery, both parents noticed how Jackson’s complexion and hair color did not match either of theirs and Mr. Smith began to question his wife’s fidelity. Jackson almost seemed as though there was an absence of color in his hair and skin. After further examination the physician informed Mr. and Mrs. Smith that Jackson had Oculocutaneous albinism. The two were confused because albinism is an autosomal recessive disorder and there was no family history of the disease causing Mr. Smith to question his wife’s fidelity a second time.

The Smith’s were distraught at first but after further counseling about albinism their minds were eased. Jackson was able to leave the hospital with his parents. The first nine months of Jackson’s life were uneventful. He was growing and developing just like any other infant would, but after those months had passed Jackson began to be afflicted by frequent and unexplainable fevers. Jackson’s parents frequented the local after hour’s clinic to get antibiotics for various bacterial infections assumed to be the source of the fevers. After a few more months of strange fevers Jackson’s mother decided to take him in to their family pediatrician. At 1 year of age, Jackson appeared to be a healthy baby boy, but the pediatrician ordered a CBC test to ensure that Jackson did not have any diseases associated with albinism.

The pathologist voiced concern about the appearance of his granulocytes—neutrophils, eosinophils, etc. Under the microscope he observed abnormally large granules in Jackson’s leukocytes. Electrophoresis was run to check gamma globulin counts and the report showed hypergammaglobulinemia. Laboratory findings also indicated neutropenia. To rule out any other forms of immunodeficiency the pathologist suggested that a FACS be run. The pathology report came back two days later reading normal levels of T cells, B cells, and Natural Killer cells. His hematocrit was also at a normal level.

<table>
<thead>
<tr>
<th>WBC</th>
<th>5300 μl⁻¹</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophils</td>
<td>1200 cells μl⁻¹</td>
<td>Mildly decreased</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>68%</td>
<td>Normal</td>
</tr>
<tr>
<td>Monocytes</td>
<td>8%</td>
<td>Normal</td>
</tr>
</tbody>
</table>

The physician suspected Chediak Higashi syndrome, but in order to confirm this suspicion she ordered genetic testing. The results showed over 40 mutations in the LYST gene. The LYST gene is responsible for normal trafficking of lysosomal regulator proteins. With a large number of mutations present in Jackson’s gene, lysosomal trafficking regulator proteins are not functioning resulting in abnormally large granules within granulocytes.

Reluctantly, the pediatrician called Jackson’s parents into her office. She informed them that Jackson had been misdiagnosed with albinism as an infant and in fact had the even more rare Chediak Higashi Syndrome. Mr. and Mrs. Smith were immediately concerned about Jackson’s prognosis. The pediatrician informed them that Jackson’s best shot was a bone marrow transplant because he had not yet reached the accelerated phase of CHS.

That afternoon HLA-typing was conducted on Jackson’s siblings. His 6-year-old sister matched for class Ia and IIs. Jackson’s immune system was ablated with cyclophosphamide and total body irradiation before receiving a bone marrow transplant. After an uneventful six months of careful monitoring Jackson gets another CBC test. When the results come back showing normal levels for all WBCs including normal looking granulocytes the physician deems the bone marrow transplant a success. The transplant will alleviate Jackson’s immunodeficiency, but he is still at risk for developing the progressive neurological defects associated with Chediak Higashi Syndrome.
Chediak Higashi Background and Case Analysis:

Jackson was diagnosed with Oculocutaneous albinism a few hours after birth. Oculocutaneous albinism is characterized by an individual’s inability to produce the pigment melanin. The melanin produced by melanocytes found in your skin and eyes determines the color of your skin, hair, and eyes. In Jackson’s case a diagnosis of Oculocutaneous albinism would explain his complexion. Albinism is caused by one or more mutations in the genes that provide instructions for producing proteins involved in the production of melanin.

Oculocutaneous albinism is a form of albinism inherited in an autosomal recessive manner. This means that both Mrs. and Mr. Smith would have to have been heterozygous for one or more of the genes coding for proteins that assist in melanin synthesis. With no family history of albinism Mr. and Mrs. Smith were rightfully concerned.

The fevers that Jackson experienced could easily be brushed off because it is not unusual for infants to be affected by many fevers while they are building their immune systems. However, Jackson’s albinism provoked the family pediatrician to look further into his health in order to rule out other syndromes often associated with albinism. After running a CBC, electrophoresis, a FACS analysis, and genetic testing for mutations in the LYST gene it became clear that Jackson had Chediak-Higashi syndrome (CHS). Bone marrow aspirates are also a helpful diagnostic tool because they highlight aberrant granules.

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Chediak Higashi Syndrome is an even more rare genetic disorder than Oculocutaneous albinism. It is not unusual for CHS to be misdiagnosed as Oculocutaneous albinism in infancy. When a child with albinism begins to have recurrent fevers associated with bacterial infections a red flag should be raised and more testing should be conducted.

CHS is associated with missense or null mutations in the LYST gene. The LYST gene codes for proteins expressed in the cytoplasm of various cells; the proteins are a responsible party in the synthesis and/or maintenance of storage/secretory granules in leukocytes. The exact mechanism affected by the mutations is unknown but one potential theory is that abnormal protein trafficking within organelles may lead to the abnormal fusion of vesicles and a failure to transport lysosome to the appropriate cellular location. This gene is defective in individuals with CHS and results in the formation of megagranules within leukocytes; specifically the lysosomes of leukocytes and fibroblasts, the dense bodies of platelets and the azurophilic granules of neutrophils. Due to the mutations, the cytotoxicity of CD8+ cells and Natural Killer cells are also affected because they are no longer able to secrete lytic granules containing granzymes and perforin further compromising the individual’s innate immunity.

Children with CHS exhibit hyperpigmentation of the skin, eye, and hair resulting in an albino appearance due to the inability of melanosomes to transport pigment filled granules to epithelial cells. They bruise easily due to mutations in the LYST gene causing abnormal dense bodies in platelets. Bacterial infections are very common in children with CHS and are caused by bacteria such as Staphylococcus aureus, Streptococcus pyogenes, and Streptococcus pneumoniae infiltrating the defenses of the skin and respiratory tract. As the disease progresses peripheral neuropathy is inevitable. Treatments for CHS include prophylactic antibodies, aggressive infection management, and bone marrow transplants. Successful bone marrow transplants can allow the child to reach adolescence or adulthood before succumbing to severe neurological defects.

Fortunately, Jackson’s CHS was caught before the development of the accelerated phase that often results in lymphoproliferative syndromes similar to lymphoma. Viruses like the Epstein Barr Virus (EBV) often cause the accelerated phase. Once the accelerated phase has begun it is usually fatal. Some success has been found when a hematopoietic stem cell transplant is performed early in the development of the accelerated phase.


Questions

- Why did Jackson only begin to have frequent bacterial infections after the first nine months of his life?

- Why was Jackson's sister the first choice for a potential bone marrow donor?

- What would have occurred if Jackson experienced a graft v. host reaction after receiving the bone marrow transplant? What about host v. graft?

- What are some of the neurological symptoms that Jackson might face in the future as a result of Chediak Higashi Syndrome?
Questions & Answers

- **Why did Jackson only begin to have frequent bacterial infections after the first nine months of his life?**

  *Jackson is still equipped with passive immunity from his mother. Circulating IgG antibodies allowed Jackson to avoid any major bacterial infections in the first nine months of his life.*

- **Why was Jackson’s sister the first choice for a potential bone marrow donor?**

  *Siblings are the best choice for transplants because they are more likely than the parents to have similar class Is and class IIs.*

- **What would have occurred if Jackson experienced a graft v. host reaction after receiving the bone marrow transplant? What steps should be taken to minimize the possibility of rejection?**

  *Jackson would get a horrible rash and severe muscular atrophy. HLA-typing should be conducted on all of Jackson’s siblings in search of a close match. Jackson’s immune system should also be ablated by the use of cyclophosphamide and total body irradiation before receiving the bone marrow transplant.*

- **What are some of the neurological defects that Jackson might develop in the future as a result of Chediak Higashi Syndrome?**

  *As a result of the successful bone marrow transplant Jackson will most likely survive to adolescence or adulthood and will develop neurological defects like cerebellar ataxia, central nervous system atrophy, seizures, peripheral neuropathy, and cognitive defects.*