Klinefelter Syndrome and Chronic Myeloid Leukemia: Coincidence or Connection?

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Abstract

Klinefelter syndrome (KS) and chronic myeloid leukemia (CML) both involve genetic abnormalities. In order to investigate a connection between the conditions, a combination of research and relevant case studies has been examined. The possibility of a connection between the two could lead to important medical and genetic discoveries, as well as improved and prolonged life for patients diagnosed with these two conditions.

Key words: chronic myeloid leukemia, klinefelter syndrome, genetics, chromosomes, hematology, cancer

Case Study

A 22-year-old male presents with splenomegaly. A history of delayed sexual development is noted. After routine hematologic testing, a tentative diagnosis of chronic myeloid leukemia (CML) is made. Further cytogenetic testing confirms the presence of a translocation between chromosome 9 and chromosome 22. Additional analysis of the patient's karyotype revealed the existence of two X chromosomes and one Y chromosome. The patient was subsequently diagnosed with Klinefelter syndrome. Treatment for CML included hydroxyurea and imatinib mesylate. After two years of treatment, the patient's BCR-ABL baseline went from 97% to 0.007%. The patient achieved full molecular and hematologic remission.

Introduction

Klinefelter Syndrome

Klinefelter syndrome is a disorder that can affect sexual and physical development, as well as cognition and intelligence. "The approximate incidence for Klinefelter syndrome is 1 in 500 to 1,000 males" (Mader & Windelspecht, 2013), making Klinefelter syndrome (KS) the most common sex chromosome disorder (Eberl, et al, 2005). KS occurs as an error of nondisjunction during gametogenesis, resulting in at least one extra X chromosome. Other variants include two or more X chromosomes, or additional X chromosomes in only some cells.

Symptoms. Symptoms can vary widely; the most common symptoms are hypogonadotropic hypogonadism (reduced function of the testes due to lack gonadotropin), lack of facial and body hair, and learning disabilities. Other symptoms include elongated arms and legs, feminine features, gynecomastia (enlarged breasts), and mental retardation. The severity of the disease increases with the amount of X chromosomes present. With the rare exception of some men with mosaic Klinefelter syndrome (KS), all men with KS are unable to reproduce due to underdeveloped testes.

Diagnosis. Klinefelter syndrome (KS) is present at birth, but early diagnosis is not common. "Because most boys with Klinefelter syndrome appear similar to boys with normal karyotypes, the disorder typically is identified in adulthood, when infertility or gynecomastia are common presentations" (Wattdendorf & Muenke, 2005). Diagnostic methods utilized for diagnosing KS include karyotype examination and hormone testing. By inspecting an individual's chromosomes using a karyotype, additional X chromosomes can be easily identified. Hematologic microscopy can reveal sex chromosome abnormality with the presence of Barr bodies in a male specimen. Barr bodies are inactivated X chromosomes and are typically found only in women.

Treatment. Klinefelter syndrome is not a life-threatening condition; however, some patients receive treatment to manage associated symptoms. Some men take testosterone to improve muscle mass and sex drive. Testosterone is also taken to decrease the risk of osteoporosis, due to low bone mineral density.

Chronic Myeloid Leukemia

Chronic myeloid leukemia (CML) is a type of cancer that causes an overproduction of white blood cells in the myeloid cell lineage. A defect in the hematopoietic stem cell causes abnormal proliferation of myeloid cells. "CML is a disease of middle age with manifestation peak in 40-50 years old" (Andreieva, et al, 2016). The bone marrow, where blood cells normally mature, becomes packed with myeloid cells at various stages of maturity. As the disease progresses, the peripheral blood reflects this increase. Cells in the myeloid lineage typically affected in CML include neutrophils, basophils, eosinophils, which are all classified as granulocytes. These cells play very specific and important roles in the human immune system. Neutrophils fight bacterial infection by phagocytosis. Basophils mediate inflammatory responses, such as anaphylactic shock. Eosinophils protect against parasites and play a role in allergies and inflammation. Due to these three cell types being overproduced, the normal numbers of monocytes and lymphocytes are decreased. When decreased, monocytes cannot help fight bacterial infections and lymphocytes cannot fight against viruses and produce normal amounts of antibodies.

The granulocyte precursors include myeloblasts, promyelocytes, myelocytes, metamyelocytes, and band neutrophils. Only band neutrophils are functional; the rest are not. Infiltration by these immature cells into the peripheral blood leaves no room for mature, functioning cells and therefore impairs the normal immune response. Unique to chronic

myeloid leukemia (CML) is a phenomena called a myelocytic bulge, which is a higher number of myelocytes in the peripheral blood than any other immature cell type. Immature red blood cells (RBCs) can also become present in peripheral blood as CML progresses because there is not enough room in the bone marrow for normal RBC production and maturation. Therefore, immature RBC forms enter circulation earlier than normal. This can cause anemia in patients in later stages of CML. Platelet counts also increase as the disorder progresses, which can lead to blood clots and bleeding.

Symptoms. Chronic myeloid leukemia (CML) typically presents between 50 and 70 years of age, however, it can present in younger or older individuals. There are three general stages of CML: chronic, accelerated, and acute. The chronic phase is typically asymptomatic with less than 10% myeloblasts (blasts) in the bone marrow. This phase can last anywhere from three to five years. The accelerated phase involves symptoms such as fatigue, weight loss, and bone pain due to fibrosis; the accumulation of fibroblast cells in the bone marrow. Other symptoms include swelling of the liver, spleen, and lymph nodes as a result of white blood cells infiltrating extramedullary sites. A distinguishing characteristic of the accelerated phase is a high increase of basophils. If an increase of basophils is not seen on peripheral smear, a diagnosis of CML should be questioned. The last stage of CML is called the acute phase or "blast crisis" phase. This phase is technically classified as an acute leukemia because the percentage of blasts has surpassed 20%. This acute leukemia derives most commonly from the myeloid cell lineage, although it can also become an acute lymphoid leukemia as well. Common physical symptoms associated with blast crisis include sepsis, bleeding, and infection due to a predominance of immature blast cells and a severe decrease in normal,

mature white blood cell types. Normal ranges and ranges for CML patients are summarized in Appendix A. (See Appendix A: Table 1).

Diagnosis. Chronic myeloid leukemia (CML) can be diagnosed in a variety of different ways. The first method most commonly used is the inspection of a peripheral blood smear and performing a white blood cell differential. Additional methods are required, however, because the peripheral blood smear in CML can look very similar to a benign leukocyte proliferation called leukemoid reaction. Another method used to confirm diagnosis of CML is cytogenetics; the analysis of an individual's karyotype. A translocation between chromosomes 9 and 22, which is denoted as t(9;22), produces a new chromosome 22, referred to as the Philadelphia chromosome (Ph^1). It is found in 90-95% of patients with CML (McKenzie & Williams, 2010). This translocation causes an abnormal gene fusion between the BCR gene on chromosome 22 and the ABL gene on chromosome 9, denoted BCR/ABL. This abnormal gene fusion causes abnormal activity of the enzyme tyrosine kinase, which plays an important role in cell proliferation and differentiation. After identifying this translocation, polymerase chain reaction can be used to determine the amount of BCR/ABL in an individual's cells, and therefore calculate what is referred to as a baseline percentage, which is used to assess the patient's molecular response to treatment.

Treatment. Treatments for chronic myeloid leukemia (CML) are very effective. If a person has the 9;22 translocation, a targeted therapy called imatinib mesylate (imatinib) inhibits the activity of the abnormal tyrosine kinase, thereby preventing overproliferation. "Results of a 5-year study using imatinib indicate that 96% of patients have a complete hematologic response by 12 months and 98% at 60 months" (McKenzie & Williams, 2010). One drawback to imatinib is that resistance can develop if a patient is given a low dose over

long periods of time. Second generation tyrosine kinase inhibitors (TKIs) must then be utilized.

Hydroxyurea is also used to reduce high white blood cell counts. Hydroxyurea is an inhibitor of DNA synthesis and acts by blocking cell division and marrow precursor maturation (Hillman, et al, 2011). Leukapheresis can also be used to eliminate excess white blood cells by physically removing them in a process similar to blood donation. Bone marrow transplants may be necessary in extreme cases.

For patients without the 9;22 translocation, prognosis is markedly worse because the treatments available are less targeted. Hydroxyurea, leukapheresis, and/or bone marrow transplantation can be used to help halt disease progression. Patients in the accelerated and acute phases have worse prognoses than patients in the chronic phase because of the intensity of disease progression.

Discussion

Case 1 (Primary)

A young adult male is diagnosed with classic Klinefelter syndrome (KS) and chronic myeloid leukemia (CML) with the presence of the 9;22 translocation in the chronic phase. Treatment with hydroxyurea and imatinib mesylate (imatinib) was successful; hematological remission was achieved in two months and full molecular remission was achieved within two years. The patient's BCR/ABL baseline at diagnosis was 97%. After two years, this baseline was at a remarkable 0.007%. The authors of this case hypothesize that chromosomal aberrations predispose stem cells to further genetic instability leading to clonal evolution of hematological disorders (Chennuri, et al, 2014). Furthermore, some various other congenital disorders are associated with an increased risk for leukemia; these including Klinefelter

syndrome (McKenzie & Williams, 2010). While the study focuses on the success of imatinib treatment in CML patients both with and without KS, it also suggests the possibility of a link between CML and KS, whether genetic or otherwise.

Case 2

In a case published in 2014, a 35-year-old male patient presented with fatigue, enlarged spleen, and high white blood cell count of 133,000/microliter. A bone marrow biopsy confirmed chronic myeloid leukemia (CML). Cytogenetic results revealed a BCR/ABL baseline of 94%, an extra X chromosome, and a 9q34.1 deletion. The extra chromosome confirmed Klinefelter syndrome (KS), although it is unclear if the patient was aware of this beforehand. The 9q34 deletion, also known as Kleefstra syndrome, is a rare genetic disorder characterized by intellectual disability, often accompanied by a spectrum of complex physical and clinical features (Kleefstra syndrome Community). The patient also had a history of tuberculosis. Imatinib mesylate treatment began after diagnosis and the patient's blood and bone marrow was normal (hematologic remission) in three months. Lack of significant molecular response within six months led to the discovery that the patient was taking rifabutin, a tuberculosis medication, with imatinib mesylate (imatinib). After increasing the amount of imatinib, the patient still did not show substantial molecular response (normal karyotype) and was then started on a second generation tyrosine kinase inhibitor. Molecular remission was finally achieved, but the patient continued "to have a suboptimal molecular response with fluctuating levels of BCR-ABL_1 transcripts in peripheral blood PCR studies" (Chakraborty, et al, 2014).

This case is both different and noteworthy because the patient had two chromosomal abnormalities in addition to KS. Is there an increased risk for hematologic malignancy for

patients with multiple genetic defects? Could this be the reason the patient's baseline percentage was still shifting at the end of this study? In addition, what role could tuberculosis play? This study poses many questions which are worthy of further investigation.

Case 3

A third case involves a 32-year-old male presenting with weakness, skin pallor, weight loss, and enlarged spleen. Initial hematologic testing revealed a high white blood cell count of 126,500 per microliter and a high hemoglobin of 39 g/dL. Analysis of plates from a bone marrow biopsy and karyotype showed the presence of mosaic Klinefelter syndrome (only some of the cells are XXY) and the 9;22 translocation associated with chronic myeloid leukemia (CML). However, a few of the metaphase plates analyzed did not show the 9;22 translocation. The patient was started on hydroxyurea and a second generation tyrosine kinase inhibitor. Total molecular molecular remission was accomplished in 11 months.

The first important aspect of this case to address is the mosaic KS; does the absence of the 9;22 translocation mean that some of the patient's cells do not carry the tyrosine kinase abnormality? If so, does this affect the success of treatment or explain the use of a second generation tyrosine kinase inhibitor versus imatinib mesylate? Does mosaic KS put a man at increased risk of leukemia? These are questions to be addressed with further case studies involving KS and CML.

Case 4

The last case study to be addressed involves a 20-year-old man with acute promyelocytic leukemia (APL) and a 32-year-old man with chronic myeloid leukemia (CML).

The patient with APL, after hematologic testing, had a high white blood cell count of 300,000 per microliter. Cytogenetic testing showed the patient had a translocation between chromosomes 15 and 17, as well as two X chromosomes. The patient began traditional APL treatment, and achieved complete remission. However, the patient relapsed after 33 months. Further cytogenetic analysis revealed the patient also had a trisomy 8. Despite further treatment and stem cell transplantation, the patient relapsed again and died.

After hematologic testing, the patient with CML, showed a high white blood count of 157,000 per microliter and was characterized as being in the accelerated phase of CML. Cytogenetic testing showed an extra X chromosome and the Philadelphia chromosome (translocation 9;22). Imatinib was prescribed, but was stopped several times because the patient's platelet count could not be stabilized within the normal reference range. The disease progressed to the acute phase with myeloid blast crisis, now technically an acute myeloid leukemia (AML), and began treatment with a second generation tyrosine kinase inhibitor along with AML induction therapy. Unfortunately, the patient expired due to sepsis.

This case features two men with KS with two different types of leukemia; does this imply a connection between KS and leukemia in general? Did the APL patient having a trisomy 8 contribute to his poor prognosis? CML and APL usually have favorable prognoses; could KS play a role in prognosis? Long-term follow up studies are needed to define the prognosis of leukemia in patients (Behir, et al, 2016), more specifically in patients with KS.

Discussion of Cases. A striking discovery is the age of the patients in these case studies. Chronic myeloid leukemia (CML) typically begins between the ages of 50 and 70; all of the patients in the aforementioned case studies were under 50 years of age. While CML can affect younger individuals, it is interesting that these patients were affected by CML earlier in life in

addition to being diagnosed with Klinefelter syndrome (KS). According to the National Cancer Institute's Surveillance, Epidemiology, and End Results Program, 9.3% of CML cases occur in ages 35 to 44 and 7.4% from ages 20-34 (National Cancer Institute). Genetic susceptibility could play a role in the early progression of CML. Could KS play a role in the development of other genetic defects, leading to CML or other white blood cell malignancies? This is an area of research that should be examined more closely, with strict guidelines to eliminate interferences.

Conclusion

If a link between choromosomal abnormality and cancer could be established, this could play a role in earlier diagnosis for cancer, better and more targeted therapies, or even cures. Patients with Klinefelter syndrome could be evaluated periodically for the emergence of CML or other leukemias. An idea to begin research into this possible connection would be to screen all patients with CML for any and all chromosomal defects and establish case studies to promote further research and examination. The field of medical science is constantly evolving and it is never known what potentially new discovery could lead to the next groundbreaking treatment or cure.

A connection between Klinefelter syndrome and chronic myeloid leukemia is conceivable, based on genetic susceptibility of patients with other chromosomal abnormalities and the young age of CML patients with KS. The need for more research into this possibility is imperative for current patients undergoing treatment, as well as future patients.

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Appendix A

Table 1: Hematology Values Associated with Chronic Myeloid Leukemia

Cell Type	Normal Range (per microliter)	CML Ranges (per microliter)
Total WBC count	4,500-11,000	50,000-200,000
Total RBC count	4,500,000-5,500,000	Normal in chronic phase, decreased in blast crisis
Total PLT count	150,000-450,000	Increased
Neutrophils	40-80%	Decreased
Lymphocytes	25-45%	Decreased
Monocytes	2-10%	Decreased
Eosinophils	0-5%	Increased
Basophils	0-2%	Increased
Myeloblasts	0%	<10% in chronic phase, 10-19% in accelerated phase, >20% in blast crisis
Promyelocytes	0%	Increased
Myelocytes	0%	Increased
Metamyelocytes	0%	Increased
Normoblasts	0%	Increased in accelerated to blast crisis