Chronic myeloid leukemia

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Introduction and epidemiological aspects:

Chronic Myeloid Leukemia (CML) is a clonal hematopoietic stem cell disorder. It is slowly progressive and is associated with consistent chromosomal abnormality. It is an unusual disease as only a single lesion in the DNA is required, this is the translocation of genetic material between chromosomes 9 and 22 resulting is formation of the Philadelphia chromosome. CML accounts for 15% of all leukemia cases and is more prevalent in men. The median age of onset is 40-60 years meaning we see increased incidence with age. CML is not inherited, however in 5% of cases 2 or more members of the same family will be affected, these cases are known as familial myeloid leukemia and are a result of genetic mutations within the sperm/egg that can lead to the child being predisposed to development of cancer, however the actual prevalence of this is not known as progress is still being made in this field. This predisposition may explain the number of patients that have the BCR-ABL oncogene but no Philadelphia chromosome present and the even smaller number of cases in which the patient has neither.

Aetiology:

Most cases of Chronic myeloid leukemia develop because of the translocation of genetic material between chromosomes 9 and 22, this results in the formation of the Philadelphia chromosome which contains the oncogene BCR-ABL, this oncogene encodes a BCR-ABL protein, this protein is a constitutionally activated tyrosine kinase that activates transduction pathways that prevent apoptosis and stimulates hematopoietic cell proliferation. However, when the BCR-ABL gene is formed abnormally (via chromosome 9 and 22 translocation) we see harmful proliferation of platelets as well as less functional leukocytes, this results in a buildup of blasts in the bone marrow leaving less room for functional, healthy hematopoietic cells. As previously mentioned, some patients have the BCR-ABL oncogene however no Philadelphia chromosome, in these cases it is thought that the oncogene had been formed because of other mutations. In even rarer cases patients have neither oncogene nor the Philadelphia chromosome so it is thought that other oncogenes initiate CML development. The only known environmental risk factor for CML is exposure to high doses of radiation. When cells are exposed to ionizing radiation the atoms or molecules that they contain may lose an electron leading to the formation of a free radical. Free radicals are highly reactive chemicals formed due to the loss or gain of an electron, they can be naturally formed and play vital roles in cellular processes however an abundance of free radicals can result in damage to the cells major components including membranes and more importantly DNA, this DNA damage can result in translocation which is an initiating factor in the oncogenesis of Chronic Myeloid Leukemia.

Pathogenesis:

The pathogenesis of Chronic Myeloid Leukemia (CML) is intricately linked to a specific chromosomal abnormality, the Philadelphia chromosome, and the ensuing molecular events that drive the disease. This clonal hematopoietic stem cell disorder initiates with a cascade of genetic changes that ultimately lead to the uncontrolled proliferation of immature white blood cells. The process commences with chromosomal breakage, a pivotal event that can be triggered spontaneously or induced by external factors such as ionizing radiation. The ensuing gene translocation involves the exchange of genetic material between chromosomes 9 and 22. Notably, chromosome 9 harbors the ABL gene, while chromosome 22 carries the BCR1 gene. The translocation results in the fusion of these genes, leading to the creation of the Philadelphia chromosome, a distinctive feature of CML. Within this altered chromosome, the BCR-ABL gene emerges, encoding the BCR-ABL protein, a potent tyrosine kinase. This protein assumes a crucial role in various signaling pathways governing fundamental cellular processes, including growth, differentiation, metabolism, and apoptosis. In the context of CML, the BCR-ABL1 protein exhibits heightened tyrosine kinase activity, disrupting the delicate balance of cell regulation. This aberrant activity manifests as increased proliferation and reduced apoptosis of hematopoietic cells, resulting in the accumulation of immature white blood cells.

As the disease progresses, it evolves through distinct phases, starting with the chronic phase, where the majority of patients are diagnosed (80-85%). During this stage, routine blood tests or physical examinations often reveal leukocytosis, characterized by elevated eosinophil, neutrophil, and basophil levels. Although blast cells constitute less than 10% of the bone marrow, there is a marked increase in granulocyte production, particularly an elevated basophil count—a distinctive feature of CML. The chronic phase is also marked by the deposition of leukocytes into the spleen, leading to splenomegaly. The enlarged spleen, influenced by extramedullary hematopoiesis, exerts pressure on the stomach, contributing to symptoms such as nausea, vomiting, and low appetite. Additionally, patients may experience fever and night sweats, attributed to the immune system's response, specifically the production of cytokines like IL-1 and TNF-d. Platelet production rises during the chronic phase, resulting in thrombocytosis. While platelets play a vital role in clotting to prevent bleeding, having excess platelets can impair normal function, posing risks of blood clots and associated symptoms like weakness, chest pain, and paresthesia.

Transitioning to the accelerated phase, there is a drastic increase in blast cells to 10-19%. This surge is driven by higher mutation rates during repetitive replication, leading to reduced cell differentiation and the accumulation of immature white blood cells. This influx of blast cells further diminishes the available space in the red bone marrow, contributing to decreased platelet and red blood cell counts. Reduced red blood cell production may result in anemia, presenting symptoms such as dyspnea, fatigue, mouth inflammation, and pale skin. Additionally, diminished platelet production leads to thrombocytopenia, manifesting as bruising, bleeding, weakness, and swollen lymph nodes. Refractory leukocytosis persists, accompanied by pruritis due to histamine production by basophils. The increase in extramedullary hematopoiesis exacerbates splenomegaly, elevating the risk of splenic rupture and splenic infarction.

The final stage, the blast phase, is characterized by a further surge in blast cells (>20%), driven by mutations impairing myeloid stem cells' ability to differentiate. Severe anemia and thrombocytopenia ensue, placing the patient in an immunocompromised state, elevating the risk of infections like pneumonia, urinary tract infections, and cellulitis. Oncologic emergencies, including leukostasis and tumor lysis syndrome, pose critical threats and contribute to the limited prognosis in this phase. About 2/3 of patients progress to acute myeloid leukemia (AML), while 1/3 develop acute lymphoblastic leukemia (ALL).

Diagnostic strategies:

Full blood count (FBC):

The first line of testing for CML will be a complete blood count, this is done to measure the patient's red blood cell, white blood cell and platelet levels from a blood sample. These results give further indication to the CML phase the patient is currently in. Patients in the chronic phase will have a normal RBC level accompanied by a heightened platelet count, however those in the blast phase will have a reduced RBC and platelet count. We see leukocytosis in CML patients with especially elevated basophil production, the number of leukocytes will be elevated in every phase of the disease however there may be a slight reduction in the accelerated phase due to accumulation of blasts in the bone marrow taking up space. A peripheral blood smear will also be done to study the proportion of blasts in the blood in comparison to fully matured, differentiated white blood cells, these will also be quantified to further establish to severity of CML in the patient.

Cytogenetic testing (bone marrow biopsy):

A bone marrow biopsy is taken from the patient to undergo cytogenetic testing, this can help us identify if the Philadelphia chromosome was the initiating factor in the development of CML. The sample is taken from the pelvis of the patient and stained; it is then examined under a microscope to identify if the Philadelphia chromosome is present in the bone marrow cells.

Fluorescent in situ hybridization (FISH):

FISH testing is a more sensitive cytogenetic test and may be used if the Philadelphia chromosome is not detected in initial biopsy examinations. FISH testing is also able to identify if the BCR-ABL1 gene is present.

Reverse transcriptase-polymerase chain reaction (qPCR):

The most efficient and highly sensitive method of cytogenetic testing is qPCR, it is used to identify if the BCR-ABL1 gene is present among bone marrow cells as well as measuring the quantity of cells that contain the gene, this can be done even if the Philadelphia chromosome cannot be detected.

Ultrasound/abdomen CT:

Splenomegaly is a vital indicator of CML as deposits of leukocytes into the spleen can cause enlargement and even splenic rupture. An ultrasound or CT of the abdomen allows us to look at the shape/size of the spleen to see if there are any abnormalities that indicate CML.

Disease progression/monitoring:

The tests used to diagnose cml are also used to monitor progression of the disease. This also provides further insight into response to the treatment the patient is being given; allowing any changes to be made if the response is not what is expected. Once treatment has begun patients will have a full blood count done every 2 weeks, if the levels begin to return to normal then this indicates that they are responding well to treatment. Further abdominal CT/ultrasounds will also be done to monitor rate of enlargement in the spleen.

Depending on the patient they will have a qPCR test done on a blood sample every 3-6 months. The results will tell us the number of cells containing the BCR-ABL1 gene present in the blood. The patient will then be categorized from MR1-5 depending on the amount of BCR-ABL1 containing cells found in the sample. This is also used to determine what percentage of cells in the blood sample contain the Philadelphia chromosome, the patient is then given a level of cytogenetic response based on this percentage.

Prevention and possible outcomes:

Preventing CML involves minimizing exposure to radiation and cancer- causing chemicals. Early detection via routine check-ups and genetic screenings remains crucial for timely intervention. Targeted therapies, especially tyrosine kinase inhibitors, have significantly improved prognosis. While many patients achieve long-term remission with proper treatment, advanced stages may lead to a less favorable prognosis, including the risk of death. Continued research is essential for developing more effective treatments and improving outcomes, particularly in cases with higher risk factors such as ionizing radiation exposure.

Treatments:

Tyrosine kinase inhibitor therapy:

This treatment uses TKIs to prevent the BCR-ABL1 protein from sending growth signals to its receptor, this protein stimulates the dangerous proliferation of haemopoietic cells. The most common TKI used is imatinib, however this may be changed if you are not responding well to treatment or are having severe side effects. You may take TKIs along with chemotherapy in more severe cases of CML.

Chemotherapy:

Patients in the blast phase will require rounds of chemotherapy, it may also be given whilst awaiting diagnosis to reduce the number of white blood cells as well as before a bone marrow transplant. The chemotherapy drug most used to reduce leukocytosis is known as hydroxycarbamide. Patients being treated with chemotherapy in the blast phase will go through two treatment phases, the first being remission induction where you will be given at least 2 types of chemotherapy drugs to destroy leukemia cells, patients may also be given TKIs at the same time. The second phase is the consolidation phase in which the patient is given a combination of drugs such as Amsacrine and Etoposide to prevent CML from returning.

Some patients may undergo maintenance treatment for up to 2 years after to ensure long term remission, the drugs given are azacytidine and decitabine.

Immunotherapy:

Although not as common anymore due to developments in medicine; inferon therapy can be used to reduce the growth and division of cancer cells, inferon-alphas mimic inferons that are substances our immune system naturally produces. Immunotherapy is given by injection daily.

Stem cell and bone marrow transplant:

Patients in the accelerated/blast phase or those not responding well to treatment may be offered a stem cell transplant to replace damaged blood cells. The transplant usually follows a high dose of chemotherapy that kills leukemia cells, however damages healthy blood cells. During the transplant you will have donor cells enter your bloodstream intravenously that find their way back to the bone marrow where they begin to help slowly recover. The stem cell transplant uses stem cells from the bloodstream whereas a bone marrow transplant takes stem cells directly from the bone marrow, however bone marrow transplants are less commonly used.

Future aspects of diagnosis and treatment:

The future prospects in the diagnosis and treatment of Chronic Myeloid Leukemia (CML) are promising, driven by advancements in medical research and innovative therapeutic approaches. With the evolving understanding of the molecular and genetic basis of CML, personalized medicine is gaining prominence. Targeted therapies, such as tyrosine kinase inhibitors (TKIs), have revolutionized the treatment landscape, offering more effective and well-tolerated options. Ongoing research focuses on refining existing therapies and developing new agents to overcome resistance mechanisms and enhance long-term outcomes.

Moreover, in the study of familial myeloid leukemia, recent developments signify a growing understanding of the genetic predispositions and familial clustering associated with myeloid disorders. Advances in genetic screening technologies have enabled the identification of familial predispositions to myeloid malignancies, shedding light on inherited genetic mutations that may elevate the risk of developing leukemia within families. Researchers have identified specific germline mutations, such as in genes like RUNX1, CEBPA, and DDX41, which play crucial roles in familial myeloid leukemia. The exploration of these genetic factors not only enhances our comprehension of the disease's hereditary aspects but also provides valuable insights for early detection and risk assessment in familial cases.

Summary:

Chronic Myeloid Leukemia (CML) is a clonal hematopoietic stem cell disorder characterized by the presence of the Philadelphia chromosome, resulting from a translocation between chromosomes 9 and 22. While not inherently hereditary, familial myeloid leukemia, representing 5% of cases, suggests a genetic predisposition. The BCR-ABL1 oncogene, formed due to this translocation, encodes a constitutively activated tyrosine kinase, leading to abnormal cell proliferation and impaired differentiation. Environmental risk factors include exposure to high doses of radiation. Diagnostic strategies involve comprehensive blood tests, cytogenetic testing, fluorescent in situ hybridization (FISH), and reverse transcriptase-polymerase chain reaction (qPCR). The disease progresses through chronic, accelerated, and blast phases, each with distinct clinical manifestations. Treatment modalities include tyrosine kinase inhibitors, chemotherapy, immunotherapy, and stem cell/bone marrow transplants. Ongoing research in personalized medicine and the study of familial myeloid leukemia holds promising prospects for refining existing therapies and improving long-term outcomes.

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