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Acute Leukemia Clinical Presentation

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1. Introduction

Acute leukemias are highly malignant neoplasms and are responsible for a large number of haematopoietic cancer-related deaths (Jemal et al 2006). Although the survival rates have improved remarkably in the younger age group, the prognosis in older patients is still poor (Redaelli et al 2003).

The clinical presentation of acute leukemia results from infiltration of bone marrow or extramedullary sites by blasts. As a result, initial symptoms may be due to the presence of anemia, neutropenia, or thrombocytopenia. Patients generally present with nonspecific complaints including weakness, lethargy, fatigue, dyspnea, fever, weight loss, or bleeding. Blasts may also infiltrate organs or lymph nodes, resulting in hepatosplenomegaly or adenopathy. Bone marrow infiltration with blasts can result in bone pain. Mucosal bleeding, petechiae, ecchymosis, and fundal hemorrhages may occur as a result of thrombocytopenia.

Patients with acute promyelocytic leukemia (APL) characteristically present with coagulopathy and signs of disseminated intravascular coagulation (DIC). It should be noted, however, that rapid cell turnover can result in DIC in any form of acute leukemia.

In acute monocytic leukemia the common findings are weakness, bleeding and a diffuse erythematous skin rash. There is a high frequency of extramedullary infiltration of the lungs, colon, meninges, lymphnodes, bladder and larynx and gingival hyperplasia.

The clinical onset of acute lymphoblastic leukemia (ALL) is most often acute, although a small percentage of cases may evolve insidiously over several months (Pui 2006). The presenting symptoms and signs correlate with the leukemic cell burden and the degree of bone marrow replacement, leading to cytopenias.

1. Marrow failure due to infiltration	
– Fatigue, pallor,	– Anemia
– spontaneous bruising	– Thrombocytopenia
– Infections, sepsis	– Neutropenia
2. <i>Infiltration of other organs</i>	
– liver, spleen, lymph nodes (particularly in ALL)	
– Lymphadenopathy	
– Hepatosplenomegaly	
– Mediastinal masses (T-ALL)	
– Gums	
– Gum hypertrophy (monocytic subtype of acute myeloblastic leukemia)	
– Bone pain, especially in children with ALL	
– Skin -Leukemia cutis	
– Soft tissue -Chloromas	
– Testis	
– Central nervous system (CNS)	
– Solid organs	
3. <i>Leukostasis</i> (only seen with WBC > 50 x 10 ⁹ /L)	
– CNS -Strokes	
– Lungs -Pulmonary infiltrates, hypoxemia	
4. <i>Constitutional symptoms</i>	
– Fevers, sweats are common	
– Weight loss uncommon	
5. <i>Other</i>	
– Exposure of substances that can initiate coagulation can cause DIC	

Table 1. Pathophysiology of the clinical manifestations of acute leukemias

2. Signs, symptoms and laboratory features of Acute Myeloblastic Leukemia (AML)

Clinical manifestations of AML result either from the proliferation of leukaemic cells or from bone marrow failure that leads to decrease in normal cells. Leukaemic cells can infiltrate tissues, leading to hepatomegaly, splenomegaly, skin infiltrates and swollen gums. As an indirect effect of the leukaemic proliferation leading to high cell destruction, hyperuricaemia and occasionally renal failure may occur. The haematopoiesis suppression leads to clinical features of anaemia, neutropenia and thrombocytopenia. Signs and symptoms that signal the onset of AML include pallor, fatigue, weakness, palpitations, and dyspnea on exertion. They reflect the development of anemia; however, weakness, loss of sense of wellbeing, and fatigue on exertion may be disproportionate to the severity of anemia. (Gur et al 1999). Easy bruising, petechiae, epistaxis, gingival bleeding, conjunctival hemorrhages, and prolonged bleeding from skin injuries reflect thrombocytopenia and are frequent early manifestations of the disease. Very

infrequently gastrointestinal, genitourinary, bronchopulmonary, or central nervous system bleeding can occur at the onset of the disease. Neutropenia translates into infectious manifestations. Pustules or other minor pyogenic infections of the skin and of minor cuts or wounds are most common. Major infections such as pneumonia, pyelonephritis, and meningitis are uncommon as presenting features of the disease, in part because absolute neutrophil counts under $500/\mu\text{l}$ ($0.5 \times 10^9/\text{L}$) are uncommon until chemotherapy is begun. Anorexia and weight loss are frequent findings. Fever is present in many patients at the time of diagnosis. Myeloid (granulocyte) sarcoma (MS) is an extramedullary tumor that occurs in 2 to 14% of cases of AML (John et al 2004); and is composed of immature and mature granulocytes or monocytes (Brunning et al 2001). These neoplasms are known by a variety of names in the literature, including granulocytic sarcoma, monocytic sarcoma, extramedullary myeloid cell tumor, myelosarcoma, myeloblastoma, and chloroma (Carneiro et al. 1984, Valbuena et al 2005). Virtually any extramedullary site can be involved by MS. Most patients with MS have a history of a myeloid neoplasm, most often AML and less often a myelodysplastic or myeloproliferative disease (Brunning et al 2001). Alternatively, MS can be the initial manifestation of AML that subsequently involves blood and bone marrow (Schmitt-Graff et al 2002). Very rarely, MS can be the only site of disease. MS is relatively more common in patients who have leukemias with prominent monocytic differentiation, such as acute myelomonocytic or monocytic leukemia and chronic myelomonocytic leukemia (Menasce et al 1999, Elenitoba et al 1996). MS manifesting as a testicular mass is uncommon and only rarely has occurred as an isolated mass. The tumors are usually localized ; they often involve bone, periosteum, soft tissues, lymph nodes, or skin. Common sites of myeloid sarcoma are orbit and paranasal sinuses. However, it should be noted that according to the WHO classification the infiltrates of any site of the body by myeloid blasts in AML patients are not classified as myeloid sarcoma unless they present with tumor masses in which the tissue architecture is effaced (Pileri et al 2008).

Blasts may infiltrate organs or lymph nodes, resulting in adenopathy or hepatosplenomegaly. Palpable splenomegaly and hepatomegaly occur in about one third of patients. Testicular infiltration is less common in AML than ALL, with an incidence of 1 to 8 % (Wiernik et al 2001). Meningeal involvement has been reported in 5 to 20% of children and up to 16% of adults with AML (John et al 2004). Leukemic blast cells circulate and enter most tissues in small numbers. Occasionally biopsy or autopsy will uncover marked aggregates or infiltrates of leukemic cells, and less frequently collections of such cells may cause functional disturbances.

3. Signs, symptoms and laboratory features of Acute Promyelocytic Leukemia (APL)

Acute promyelocytic leukaemia (APL) is a distinctive sub-type of acute myeloid leukaemia that has distinct biologic and clinical features.

According to the older French-American-British (FAB) classification of AML, based solely on morphology as determined by the degree of differentiation along different cell lines and the extent of cell maturation (Cheson et al 1990), APL is sub-typed as AML-M3. The new World

Health Organization (WHO) classification of AML incorporates and interrelates morphology, cytogenetics, molecular genetics, and immunologic markers and is more universally applicable and prognostically valid (Brunning et al 2001). APL exists as 2 types, hypergranular or typical APL and microgranular (hypogranular) APL. APL comprises 5% to 8% of cases of AML and occurs predominately in adults in midlife (Büchner et al. 1999). Both typical and microgranular APL are commonly associated with DIC (Karp et al. 1987, Gollard et al 1996, Davey et al 1986, Tobelem et al 1980). The severe bleeding diathesis associated with APL has a specific sensitivity to treatment with all-trans retinoic acid (ATRA), which acts as a differentiating agent (Licht et al 1995). High complete remission rates in APL may be obtained by combining ATRA treatment with chemotherapy (Brunning et al 2001).

4. Signs, symptoms and laboratory features of Acute Myelomonocytic (AML-M4) and Acute Monoblastic/Monocytic Leukemia (AML-M5)

Acute myelomonocytic (M4) and monoblastic/monocytic leukemia (M5), are the morphologic subtype of acute myelogenous leukemia that are most commonly characterized by weakness, bleeding and a diffuse erythematous skin rash and frequently presents with extramedullary involvement, including liver, spleen, lymph nodes, gingiva, skin, eyes, larynx, lung, bladder, meninges and the central nervous system. Involvement of the gastrointestinal tract is rare, the mouth, rectum and anal canal being the most affected sites (Lichtman et al 1995). By contrast, leukemic infiltration of the stomach has been very rarely described, and when it has, it has been mainly in children (Kasantikul et al 1989 ; Kontny et al. 1995; Domingo-Domenech et al 2000). Serum and urinary muramidase levels are often extremely high.

Neurological symptoms may occur such as, headache, nausea, vomiting, photophobia, cranial nerve palsies, pupil edema and/ or nuchal rigidity. These symptoms may result from leukostasis, but may also reveal meningeal invasion by myeloblasts or be the presenting symptoms of a "chloroma". These chloromas often have an orbital or periorbital localization, or may arise around the spinal cords causing paraparesis or " Cauda equine" syndrome. CNS leukemic infiltration occurs in 6-16% of AML (Abbott et al 2003), especially in AML-M4.

Renal insufficiency occurs seldom. It is caused by hyperuriccuria and / or hyperphosphaturia, leading to obstructing tubular deposits and oliguria/ anuria.

5. Signs, symptoms and laboratory features of Acute Lymphoblastic Leukemia (ALL)

The clinical presentation of ALL may range from insidious nonspecific symptoms to severe acute life-threatening manifestations, reflecting the extent of bone marrow involvement and degree of extramedullary spread (Pui et al 2006) (Table 2). The symptoms at onset are primarily produced by the detrimental effects of the expanding cell population on bone marrow, and

secondarily by the infiltration of other organs and by metabolic disturbances (Henderson et al 1990, Gur et al. 1999). In younger patients the anemia-induced fatigue may be the only presenting feature. Dyspnea, angina, dizziness, and lethargy may reflect the degree of anemia in older patients presenting with ALL. Approximately half of all patients may present with fever attributable to the pyrogenic cytokines, such as IL-1, IL-6, TNF, released from the leukemic cells, infections, or both. Arthralgia and bone pain due to bone marrow expansion by the leukemic cells and occasionally necrosis can be observed, although less commonly in adults compared to children. Pallor, petechiae, and ecchymosis in the skin and mucous membranes due to thrombocytopenia, DIC, or a combination of the above may be observed. ALL may present with either leukopenia (~20%) or moderate (50%–5–25 × 10⁹/L) and severe leukocytosis (10%–>100 × 10⁹/L) with hyperleukocytosis (>100 × 10⁹ /L) present in approximately 15% of the pediatric patients (Pui et al 2006). Neutropenia (less than 500 granulocytes per mm³) is a common phenomenon and is associated with an increased risk of serious infection. Hypereosinophilia, generally reactive, may be present at diagnosis. The majority of patients present with platelet counts less than 100 × 10⁹/L (75%), while 15% have platelet counts of less than 10 × 10⁹/L. Decreased platelet counts (median, 50×10⁹/L) are usually present at diagnosis and can be readily distinguished from immune thrombocytopenia, as isolated thrombocytopenia is rare in leukemia. Severe hemorrhage is uncommon, even when platelet counts are as low as 20×10⁹/L, and infection and fever are absent. Coagulopathy, usually mild, can occur in T-cell ALL and is only rarely associated with severe bleeding. More than 75% of the patients presents with anemia, which is usually normochromic and normocytic and associated with a normal to low reticulocyte count. Anemia or thrombocytopenia is often mild (or even absent) in patients with T-cell ALL. Pancytopenia followed by a period of spontaneous hematopoietic recovery may precede the diagnosis of ALL in rare cases and must be differentiated from aplastic anemia.

Bone marrow is usually infiltrated with >90% blast cells. Infiltration with less than 50% blasts represents only 4% of cases. Though the distinction between lymphoblastic leukaemia and lymphoma is still arbitrary, for many treatment protocols 25% bone marrow blasts is used as threshold for defining leukaemia (Borowitz & Chan 2008). Normal trilineage haematopoiesis is consequently decreased. The classical triad of symptoms related to bone marrow failure are the following: (1) fatigue and increasing intolerance to physical exercise (caused by anaemia), (2) easy bruising and bleeding from mucosal surfaces and skin (caused by thrombocytopenia especially when platelets are <20 × 10⁹ /L), and (3) fever with infections (40% of all cases, caused by absolute granulocytopenia). Hyperleukocytic leukaemias with >100 × 10⁹ /L blast cells rarely lead to the leukostasis syndrome and catastrophic early bleeding (Porcu et al 2000). Also malaise, lethargy, weight loss, fevers, and night sweats are often present but typically are not severe. Compared to AML, patients with ALL experience more bone and joint pain. Rarely, they may present with asymmetric arthritis, low back pain, diffuse osteopenia, or lytic bone lesions [Gur et al 1999]. Children experience these symptoms more frequently than adults. Young children may have difficulties in walking due to bone pain [Farhi et al 2000]. Lymphadenopathy, splenomegaly, and hepatomegaly are more common than in AML and affect half of the adults with ALL. CNS involvement is also more common in ALL compared to AML.

Signs and symptoms	Clinical and laboratory findings
Pallor, fatigue, exertional dyspnea, CHF	Anemia
Fever (~50%), infection (<30%)	Neutropenia
Petechiae, ecchymosis, retinal hemorrhages	Thrombocytopenia
Hepatomegaly, splenomegaly (~50%), lymphadenopathy	Leukocytosis (10% of patients with WBC > 100,000)
Bone pain and joint pain (5–20%)	Leukostasis
Leukemia cutis	Mediastinal Mass (80% of patients with T-cell ALL)
Dyspnea, hypoxia, mental status changes, Cough, dyspnea, chest pain	CNS involvement (<10%)
Headache, diplopia, cranial neuropathies, Particularly cranial nerves VI, VIII, papilledema, nausea, vomiting	Testicular involvement (<1%)
Painless testicular/scrotal enlargement	Elevated prothrombin time (PT), partial thromboplastin time (PTT), low fibrinogen
Intracranial bleeding, DIC	Acute renal failure (uncommon), acidosis, hyperkalemia, hyperphosphatemia, hypocalcemia, elevated serum LDH and, uric acid level
Tumor lysis syndrome	

Table 2. Clinical features of adult acute lymphocytic leukemias

Patients may present with cranial neuropathies (most often involving the 6th and 7th cranial nerves). Nausea, vomiting, headache, or papilledema may result from meningeal infiltration and obstruction of the outflow of cerebrospinal fluid (CSF) leading to a raised intracranial pressure. Testicular involvement, presenting as a painless, unilateral mass, is noted at diagnosis in approximately 2% of boys. It is associated with infant or adolescent age, hyperleukocytosis, splenomegaly, and mediastinal mass [Farhi et al 2000]. The diagnosis of testicular involvement is made by wedge biopsies. Bilateral biopsies are necessary due to the high incidence of contralateral testicular disease [Amendola et al 1985.]

6. Central nervous system involvement

The incidence of CNS involvement in patients with AML is considerably less common than CNS involvement in both adults and children with ALL (Charles et al 2012). Early CNS leukemia occurs in 8% of patients at the time of the first diagnosis while the percentage of relapsing CNS leukemia is 10%. (Hardiono et al 2001).

Patients with CNS involvement may be asymptomatic or may have symptoms related to increased intracranial pressure (headache, nausea, vomiting, irritability). All patients newly diagnosed with ALL should have a lumbar puncture for cytologic analysis of the cerebrospinal fluid; for AML, however, this is performed only in patients with symptoms indicative of CNS involvement (Pavlovsky et al 1973). There is an association of central nervous system involvement and diabetes insipidus in AML with monosomy 7, abnormalities of chromosome 3 and inversion of chromosome 16. (Glass et al 1987; Lavabre-Bertrand et al. 2001; Harb et al 2009).

Central nervous system hemorrhage and infection are reported to cause 80% (Lazarus et al 2006) of all deaths in patients with leukemia. The intracerebral hemorrhages that are often related to intravascular leukostases and leukemic nodules, and associated with leukocyte counts more than $100 \times 10^9/L$ in peripheral blood (Phair et al 1964).

6.1. Leukemic parenchymal tumor

CNS may be affected as a solid tumors consisting of myeloid leukemic blasts called granulocytic sarcomas or chloromas (Recht et al 2003, Teshima et al 1990). The term chloroma results from the greenish color of these tumors caused by the presence of myeloperoxidase. Chloromas usually have a dural attachment although parenchymal tumors have rarely been reported. These tumors are hypercellular and avidly enhance with either cranial magnetic resonance imaging (MRI) or cranial computed tomography (CT). Neurologic findings are dependent upon location. Chloromas most often occur in bone that may result in epidural spinal cord compression, the orbit that may result in proptosis and a restrictive ophthalmopathy, or dura, which may simulate a meningioma.

6.2. Intracranial hemorrhage

Hemorrhagic complications are common in patients with acute leukemia (approximately 20%) and constitute the second most common cause of death in such patients (20% of all leukemic deaths result from intracranial hemorrhage) (Kim et al 2004, Kawanami et al 2002). Intracranial hemorrhage (ICH) is the most common hemorrhagic complication in acute promyelocytic leukemia and is not infrequent in AML and ALL (ranging in occurrence from 2-18% of all patients with acute leukemia). ICH may occur at the time of diagnosis (early hemorrhage) or subsequent to diagnosis and following initial treatment (late hemorrhage) (Cortes et al 2001). DIC, disseminated aspergillosis or mucormycosis, leukemic cell infiltration, thrombocytopenia or L-asparaginase chemotherapy-related consequences, are the most common etiologies for ICH. Both DIC (especially common in the M3 subtype of AML) and thrombocytopenia typically result in a solitary often-massive ICH whereas disseminated fungal infection and ICH occurring during neutropenia and is a result of hemorrhagic infarction. Leukemic cell infiltration occurs with extreme leukocytosis (defined as $>300 \times 10^9$ leukemic cells/L and increase the risk of multiple intracranial hemorrhages in acute leukaemia(Bunin et al 1985). L-asparaginase may induce hyperfibrinogenemia and result in cortical vein or sinus thrombosis complicated with venous infarction. Fungal-related mycotic aneurysms may also lead to ICH and would be a consideration in a patient with blood culture positive for fungus. Topographically the majority of ICH is intraparenchymal with cerebral hemorrhage more common than cerebellar. (Wolk et al 1974).

Subarachnoid hemorrhage occurs in the context of ICH, either in isolation or more frequently as more diffuse hemorrhage secondary to DIC. Spinal subarachnoid hemorrhage may occur in the context of DIC and acute promyelocytic leukemia and present primarily with back pain that migrates rostrocaudally.

Risk - factor analysis revealed that female gender, APL, leukocytosis, thrombocytopenia and prolonged PT were the risk factors for fatal intracranial hemorrhages, while other reports have suggested the significance of serum fibrinogen (Wide et al 1990).

6.3. Leukemic meningitis

Meningeal leukemia appears more often in patients with ALL than in those with AML (Lazarus et al 2006). The manner in which leukemia cells enter the CNS is a subject of controversy, but the likely source include hematogenous spread or direct spread from adjacent infiltrated bone marrow.

Meningitis in leukemia may result from leptomeningeal infiltration of tumor (LM), subarachnoid hemorrhage, chemical (treatment-related following intra-CSF instillation of chemotherapy) or infection (bacterial or fungal) (Cash et al 1987, Dekker et al 1985). The presence or absence of LM always needs to be ascertained as if diagnosed, prognosis is profoundly affected. Chemical meningitis (typically due to intra-CSF cytarabine or methotrexate and most often given intraventricularly) is temporally related to intra-CSF chemotherapy. Chemical meningitis begins one to two days after intra-CSF chemotherapy administration, It is transient typically lasting less than five days and demonstrates no evidence of infection by CSF culture. Like other meningitis syndromes, patients complain of headache, fever, nausea, vomiting, photophobia and meningismus. Notwithstanding an inflammatory CSF, chemical meningitis rapidly abates and is mitigated by oral steroids. Infectious meningitis occurs in leukemia due to immunosuppression both as a result of the underlying disease and its treatment. *Listeria*, *Candida* and *Aspergillus* are common infectious etiologies however clinical presentation differs. *Listeria* presents as a meningitis syndrome whereas *Candida* presents with a diffuse encephalopathy and multiple small brain abscesses and *Aspergillus* presents with progressive hemorrhagic stroke confined to a single vascular territory (Gerson et al 1985, Winston et al 1993).

6.4. Cerebrospinal fluid in leukemic patients

The cerebrospinal fluid findings in leukemic patients must be carefully evaluated since bacterial meningitis, abscess formation or fungal disease occur with increased frequency. Cerebrospinal fluid pleocytosis, chemical abnormalities (elevated protein and low sugar) and elevated pressure may be present in these potential complications of the disease or its therapy. Appropriate cultures and stains, are often helpful in diagnosis. Abscesses can often be detected by brain scans, electroencephalograms and arteriography.

6.4.1. Categories of CNS status at diagnosis of acute leukemia

Patients who have nontraumatic diagnostic lumbar punctures at diagnosis may be placed into 3 categories according to white blood cells (WBCs) per microliter and the presence or absence of blasts on the cytospin: central nervous system 1 (CNS1) refers to CSF with <5 WBCs per microliter with cytospin negative for blasts; Cxlink refers to CSF with <5 WBCs per microliter with cytospin positive for blasts; CNS3 refers to CSF with >5 WBCs per microliter with cytospin

positive for blasts. Children with ALL who presents with CNS disease at diagnosis (CNS3) are at high risk for treatment failure compared with patients not meeting the criteria of the CNS disease at diagnosis. Patients with Cxlink may be at an increased risk of CNS relapse, although this may not apply to all treatment regimens and can be overcome by more intensive intrathecal treatment (Burger et al 2003).

7. Testicular involvement

Involvement of the testis - one of the most common sites of relapse in acute lymphoblastic leukemia usually presents with painless enlargement of one or both testis. Testicular involvement occurs in 10% to 23% of boys during the course of the disease at a median time of 13 months from diagnosis. Occult testicular involvement is recognized in 10% to 33% of boys undergoing bilateral wedge biopsies performed during the first 3 years of treatment or at any time after cessation of the therapy (Lanzkowsky et al. 1985). In a study in which biopsies were done in boys with newly diagnosed ALL, microscopic testicular involvement was reported to be 21% (Neimeyer et al 1993). Testicular involvement of the endothelial side of the interstitium of one or both testis, leads to increased testicular size and firmness [Kay et al 1983]. Hydrocele resulting from lymphatic obstruction may also present with painless scrotal enlargement and is readily identified by ultrasonography. Overt testicular involvement may occur in any form of acute lymphoblastic leukemia, most commonly in common C-ALL, but also in T-ALL and B-ALL. Rarely it is present when ALL is first diagnosed, but most often it is a late complication and, as with meningeal leukemia, the higher the initial blood blast count is, the earlier the discovery of testicular disease is likely (Nesbit et al 1980).

8. Superior vena cava syndrome

Superior vena cava syndrome comprises the signs and symptoms associated with compression or obstruction to the superior vena cava. Patients with ALL (particularly T-ALL), may present with symptoms of cough, dyspnea, stridor, or dysphagia from tracheal and esophageal compression by a mediastinal mass (15% of patients). Compression of the great vessels by a bulky mediastinal mass also may lead to the life threatening superior vena cava syndrome (Marwaha et al 2011). A child with leukemia may experience anxiety, confusion, drowsiness and sometimes unconsciousness (Salsali et al 1969). There is facial edema, plethora, cyanotic faces. Venous engorgement of neck, chest and arm with collateral vessel and some sign of pleural effusion and pericardial effusion may be present (Rice et al 2006).

9. Skin involvement

Various cutaneous lesions can be observed in patients with acute leukemias. These include specific cutaneous lesions resulting from infiltration of the skin by the leukemic cells, charac-

teristic diseases such as pyoderma gangrenosum and Sweet syndrome, cutaneous signs of infection or hemorrhage resulting from the bone marrow dysfunction induced by the malignant process or chemotherapy.

Skin involvement may be of three types: nonspecific lesions, leukemia cutis, or granulocytic sarcoma of skin and subcutis. Nonspecific lesions include macules, papules, vesicles, pyoderma gangrenosum, or vasculitis (Bourantas et al. 1994, Nambiar Veetil et al 2009), neutrophilic dermatitis (Sweet's syndrome) (Cho K-H et al 1997, Philip R Cohen 2007), cutis verticis gyrata, or erythema multiforme or nodosum (Byrd et al 1995). Leukemia cutis lesions usually appear at the time of diagnosis of systemic disease or thereafter, but occasionally can occur before peripheral blood or bone marrow involvement (aleukemic leukemia cutis). (Christos Tziotzios et al 2011, Márcia Ferreira et al 2006). T-cell ALL may show epidermotropism and monocytic leukemia often involves the entire dermis and the superficial panniculus (Yalcin et al 2004).

10. The gastrointestinal tract

Gastrointestinal (GI) manifestations of leukemia occur in up to 25% of patients at autopsy, generally during relapse. Its presence varies with the type of leukemia and has been decreasing over time due to improved chemotherapy. Gross leukemic lesions are most common in the stomach, ileum, and proximal colon. Leukemia in the esophagus and stomach includes hemorrhagic lesions from petechiae to ulcers, leukemic infiltrates, pseudomembranous esophagitis, and fungal esophagitis. (Dewar et al. 1981) The mouth, colon, and anal canal are sites of involvement that most commonly lead to symptoms. Oral manifestations may bring the patient to the dentist; gingival or periodontal infiltration and dental abscesses may lead to an extraction followed by prolonged bleeding or an infected tooth socket. (Dean et al. 2003). The gingival hyperplasia is most commonly seen with the AML subtypes acute monocytic leukemia M5 (67%), acute myelomonocytic leukemia M4 (18.5%) and acute myelocytic leukemia M1-M2 (3.7%) (Cooper et al 2000). Enterocolitis, a necrotizing inflammatory lesion involving the terminal ileum, cecum, and ascending colon, can be a presenting syndrome or can occur during treatment. Fever, abdominal pain, bloody diarrhea, or ileus may be present and occasionally mimic appendicitis. Intestinal perforation, an inflammatory mass, and associated infection with enteric gram-negative bacilli or clostridial species are often associated with a fatal outcome. Isolated involvement of the gastrointestinal tract is rare. (Tim et al 1984).. Neutropenic enterocolitis (NE), which is a fulminant necrotizing process is a well-recognized complication of neutropenia in patients dying from hematologic malignancies especially acute leukemia as indicated by various autopsy series (Steinberg et al 1973). Proctitis, especially common in the monocytic variant of AML, can be a presenting sign or a vexing problem during periods of severe granulocytopenia and diarrhea. (Christos Tziotzios et al. 2011)

11. Respiratory tract involvement

Infectious and noninfectious pulmonary complications represent a critical problem for patients with leukemia, which itself can be the direct cause of pulmonary leukostasis, pulmonary leukemic infiltration (PLI), and leukemic cell lysis pneumopathy. These disorders are usually more frequent in patients with hyperleukocytic leukemia. Pulmonary leukostasis is characterized by occlusion of the pulmonary capillaries and arterioles by leukemic cells. Leukemic infiltration may lead to laryngeal obstruction, parenchymal infiltrates, alveolar septal infiltration, or pleural seeding. Each of these events can result in severe symptoms and radiologic findings (Potenza et al 2003, Wu et al 2008).

Pulmonary disease in leukaemia is frequent and often lethal. Lung involvement in leukaemia is primarily due to (a) leukostasis of vessels and (b) true leukaemic infiltration of interstitium and alveoli. (Majhail et al 2004, Porcu et al 2000) Clinically, leukostasis in leukaemia should be suspected in patients with unexplained fever and cardiopulmonary or cerebral dysfunction. Pulmonary leukostasis was found in about 40% of autopsy series. (Mark et al 1987). Maile *et al* 1983 noted parenchymal opacities on 90% of chest radiographs obtained shortly before death in adult patients with leukaemia. These radiologic opacities on autopsy were attributed to infections, haemorrhages, leukaemic infiltrations and edema. In addition, drug induced pulmonary infiltrates and leukoagglutinin transfusion reactions were also reported (Mark et al 1987). In spite of the above data, pulmonary leukostasis in leukaemia has been mentioned only incidentally as a cause of abnormalities on chest radiography.

12. Cardiac complications

Cardiac complications of the patients with acute leukemia are common. Most of the cardiac complications may be due to chemotherapeutics such as anthracyclins, besides anemia, infections, or direct leukemic infiltrations of the heart. Symptomatic pericardial infiltrates, transmural ventricular infiltrates with hemorrhage, and endocardial foci with associated intracavitary thrombi can, on occasion, cause heart failure, arrhythmia, and death. Infiltration of the conducting system or valve leaflets or myocardial infarction may occur. (Ashutosh et al 2002, Fernando et al 2004). Cardiac and other tissue damage as a consequence of release of eosinophil granule contents can occur in patients with leukemia, associated with eosinophilia (Kocharian et al 2006). Cardiac damage is a major determinant of the overall prognosis.

13. Urogenital involvement

The urogenital organs can also be affected. The kidneys are infiltrated with leukemic cells in a high proportion of cases, but functional abnormalities are rare. Hemorrhages in the pelvis or the collecting system are frequent, however, cases of vulvar, bladder neck, prostatic, or testicular involvement have been described.. (Quien et al 1996).

14. Musculoskeletal system

Musculoskeletal manifestations are the presenting complaint in up to 20% of patients with pediatric leukemia, (Andreas et al 2007). The main clinical osteoarticular manifestations in early leukemia include limb pain, nighttime pain, arthralgia, and arthritis. Skeletal manifestations of acute leukaemia (bone or back pain, arthritis or radiographical abnormalities of skeleton) are well described in children (Barbosa et al 2002). Arthritis can occur at any time during the course of acute leukaemia. It may lead to delay in diagnosis and therapy and any delay in therapy is associated with poor prognosis (Sandeep et al 2006). The most common clinical presentation of leukaemic arthritis is additive or migratory asymmetrical oligoarticular large joint arthritis and in some cases juvenile idiopathic arthritis. (Evans et al. 1994, Mirian et al. 2011). The joints most commonly involved are the knee, followed by the ankle, wrist, elbow, shoulder and hip. Onset of arthritis may be sudden or insidious, and parallel the course of acute leukaemia (Sandeep et al. 2006).

Arthritis as the first manifestation of acute leukaemia is however extremely uncommon in adults.

15. Hyperleukocytosis and leukostasis

Leukostasis is a syndrome, caused by clumping of leukocytes in the vasculature of the lungs and brain, often resulting in hypoxia, dyspnea, confusion, and coma, and may be fatal.

Leukapheresis is indicated in the initial management of leukostasis in patients with hyperleukocytosis in acute leukemias, particularly myeloid leukemias, or in patients who are at high risk of developing such a complication.

Adult T-cell leukemia/lymphoma is a distinct form of ALL that presents with progressive lymphadenopathy, hepatosplenomegaly, and hypercalcemia. It involves the skin, lungs, bone marrow, intestinal tract, and CNS. This disease is associated with HTLV-1 and is endemic in the Caribbean, southeastern United States, Africa, and Japan. Circulating tumor cells have a characteristic "cloverleaf"-shaped nucleus.

The risk factors for leukostasis are acute the leukaemia itself, younger age (most common in infants), certain types of leukaemia like acute promyelocytic (microgranular variants), acute myelomonocytic, acute monocytic leukaemia and T cell type of ALL. Cytogenetic abnormalities – 11q23 translocations and presence of Philadelphia chromosome are also associated with leukostasis (Porcu et al 2000). The pathogenesis of leukostasis is determined by: - 1) sluggish flow with stasis, 2) aggregation of leukaemic cells, 3) formation of microthrombi, 4) release of toxic granules, 5) endothelial damage, 6) oxygen consumption by leukocytes, 7) tissue invasion (Litchman et al 1987). Leukostasis is usually associated with counts of $>100 \times 10^9$ but acute monocytic leukaemia may present with leukostasis with counts of $50 \times 10^9/L$. 5-13% of patients of AML and 10-30% of patients of ALL will manifest with hyperleukocytosis. Earlier leukostasis was thought to be due to the presence of critical leukocrit (fractional leukocyte volume) and

increased viscosity. Although hyperleukocytosis is also common presenting feature in patients with ALL, particularly with T-cell phenotype, 11q23, and t(9;22) chromosomal rearrangements, symptomatic leukostasis is exceedingly rare [Porcu et al 2000]. While WBC count is a major factor contributing to microvessel occlusion seen with leukostasis, other features, such as activation of adhesion cell surface markers and mechanical properties of the leukemic blasts, are likely to be important. For example, the stiffness of myeloid blasts, as measured by atomic force microscopy, is 18 times that of lymphoid blasts [Rosenbluth et al 2006]. This difference in deformability of the cells may at least partially explain the increased frequency of leukostasis in AML compared to than in ALL. Presence of symptoms suggestive of leukostasis, such as headache, blurred vision, dyspnea, hypoxia, constitute a medical emergency and efforts should be made to lower the WBC rapidly. However, the role of leukapheresis to reduce tumor burden in patients with ALL and leukocytosis remains controversial.

16. Metabolic complications

Hyperuricemia and hyperphosphatemia with secondary hypocalcemia are frequently encountered at diagnosis, even before chemotherapy is initiated, especially in patients with B-cell or T-cell ALL with high leukemic cell burden. Severe metabolic abnormalities may accompany the initial diagnosis of ALL and AML (Haralampos et al 1999). Patients with high leukemic burden are at risk of developing acute tumor lysis syndrome (ATLS). Such metabolic changes may lead to the development of oliguric renal failure due to the tubular precipitation of urate and calcium phosphate crystals, fatal cardiac arrhythmias, hypocalcemic tetany, and seizures (Jeha 2001).

17. Lactic acidosis

Lactic acidosis (LA), as the presenting manifestation of acute leukemia, is rare, but potentially fatal complication of acute leukemia (Grossman et al 1983), characterized by low arterial pH due to the accumulation of blood lactate. It has been suggested that LA occurring in the setting of hematological malignancy is associated with an extremely poor prognosis [Sillos et al 2001]. Lactate, the end product of anaerobic glycolysis, is metabolized to glucose by the liver and kidneys. Because leukemic cells have a high rate of glycolysis even in the presence of oxygen and produce a large quantity of lactate, LA may result from an imbalance between lactate production and hepatic lactate utilization [Sillos et al 2001]. Several factors may contribute to the high rate of glycolysis. Overexpression or aberrant expression of glycolytic enzymes, such as hexokinase, the first rate-limiting enzyme in the glycolytic pathway [Mazurek et al 1997] allows leukemic blasts to proliferate rapidly and survive for prolonged periods [Mathupala et al 1997]. Although insulin normally regulates the expression of this enzyme, insulin-like growth factors (IGFs) that are overexpressed by malignant leukemic cells, can mimic insulin activity [Werner 1996,]. LA is frequently associated with acute tumor lysis syndrome (ATLS) and its extent is correlated with the severity of ATLS.

Typically, the patient with lactic acidosis presents with weakness, tachycardia, nausea, mental status changes, hyperventilation, and hypotension, which may progress to frank shock as acidosis worsens. Laboratory studies show a decreased blood pH (<7.37), a widened anion gap (>18), and a low serum bicarbonates.

HCT-CI weighted scores	Definitions of comorbidities included in the new HCT-CI	Comorbidity
1	Atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmias	Arrhythmia
1	Coronary artery disease - one or more vessel-coronary artery stenosis requiring medical treatment, stent, or bypass graft, congestive heart failure, myocardial infarction, or EF \leq 50%	Cardiac
1	Crohn disease or ulcerative colitis	Inflammatory bowel disease
1	Requiring treatment with insulin or oral hypoglycemics but not diet alone	Diabetes
1	Transient ischemic attack or cerebrovascular accident	Cerebrovascular disease
1	Depression or anxiety requiring psychiatric consult or treatment	Psychiatric disturbance
1	Chronic hepatitis, bilirubin > ULN to 1.5 \times ULN, or AST/ALT > ULN to 2.5 \times ULN	Hepatic, mild
1	Patients with a body mass index > 35 kg/m ²	Obesity
1	Requiring continuation of antimicrobial treatment after day 0	Infection
2	SLE, RA, polymyositis, mixed CTD, or polymyalgia rheumatica	Rheumatologic
2	Requiring treatment	Peptic ulcer
2	Serum creatinine > 2 mg/dL, on dialysis, or prior renal transplantation	Moderate/severe renal
2	DLco and/or FEV1 66%-80% or dyspnea on slight activity	Moderate pulmonary
3	Treated at any time point in the patient's past history, excluding nonmelanoma skin cancer	Prior solid tumor
3	Except mitral valve prolapse	Heart valve disease
3	DLco and/or FEV1 \leq 65% or dyspnea at rest or requiring oxygen	Severe pulmonary
3	Liver cirrhosis, bilirubin > 1.5 \times ULN, or AST/ALT > 2.5 \times ULN	Moderate/severe hepatic

Table 3. Definitions of comorbidities and HCT-CI scores included in the HCT-CI

18. Comorbidity

Many factors have been studied to predict outcome and allocate treatment in acute leukemia. The best established prognostic factors are karyotype and age. However, comorbidity may play an important role in the outcome.

A comprehensive assessment including performance status, evaluation of comorbidities and abilities to perform activities of daily living, geriatric depression scale in elderly patients has been proven to be useful in detecting treatment-related changes in older cancer patients and has been recommended to be incorporated into clinical outcome analysis. An index developed specifically for patients with hematologic malignancies has been developed: the Hematopoietic Cell Transplantation-Specific Comorbidity Index (HCT-CI) presented in Table 3 (Sorró ML et al 2005). This index captures comorbidities that predict non-relapse mortality in patients considered for allogeneic transplant and also proved to be a helpful tool for defining comorbid conditions in elderly untreated AML patients. (Novotny J et al 2009; Sorró ML et al 2007). Modifications such as modified EBMT risk score have been developed and evaluated for ALL patients (Terwey T et al, 2010).

Comorbidity scoring is currently still under the investigation in many cooperative groups. It is important to bear in mind that when translating the results from clinical trials into treatment decision-making for the individual patient, many patients with e.g. „unacceptable“ renal, cardiac or hepatic abnormalities are generally not included into clinical trials. By such approach at least 20-30% of younger patients and more than 50% of elderly patients with AML are excluded and have not been reported in any results. Because of that it would be important to propose comorbidity score for all leukemia patients and to evaluate how many of the patients are able to receive standard therapy and stem cell transplantation, how many of them are candidate for low-intensity treatment and supportive care.

While acute leukemia patients depend on the expert recommendations from their physicians, knowledge of clinical presentation and patient's related prognostic factors can help to improve treatment decision and to identify patients who would benefit most from either intensive or low-intensive treatment or even best supportive care alone.

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