ABSTRACT

Leukaemia is a malignant neoplasm affecting the hematopoietic system. Incidence averages 4-4.5 cases/year/100,000 in children younger than 15 years. Leukaemia cutis is an aggressive leukaemia cell infiltration into the epidermal, dermis, and sub-cutis layers. The incidence is infrequent, can occur in all types of leukaemia. A 12-year-old boy, referred with pale, intermittent fevers, gum bleeding from 10 months and lumps on the skin from 2 months before admission. Physical examination was showed gingival hyperplasia, multiples mass of 1-3 cm in diameter in the head, neck, thoracic, abdominal and hand region, hepatomegaly and splenomegaly. The nutritional status was severe malnutrition. Laboratory examinations showed leukocytosis, mild anaemia, and severe thrombocytopenia. Bone marrow aspiration occurs AML suspicion with 10% myeloblast and 5% monoblast. Skin biopsy suggests cutaneous infiltration by myeloblast and monoblast. A patient diagnosed with acute myeloblastic leukaemia, leukaemia cutis, and severe malnutrition — chemotherapy with guided by non-lymphoblastic acute leukaemia protocol. After 4 months of chemotherapy patients and families decided not to continue chemotherapy and only supportive therapy such as transfusion. The patient passed away 9 months after the diagnosis. Leukaemia cutis is uncommon as the presenting feature of AML and is associated with an unfavourable prognosis. There is no specific treatment for cutaneous leukaemia other than palliation and symptomatic relief. The 2-year survival rate for the unfavorable prognostic group it is 10-20%.

Keywords: leukaemia cutis, acute myeloblastic leukaemia, malnutrition, children.

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INTRODUCTION

Malignancy is often found in childhood. Acute leukaemia is 30-40% of all fatalities in childhood. Incidence averages 4-4.5 cases/year/100,000 in children younger than 15 years. Acute lymphoblastic leukaemia account for about 75% of all cases, acute myeloid leukaemia (AML) for about 20% and most of the remaining leukaemia is of the chronic myeloid form.
The cause of leukaemia is not known with certainty, allegedly associated with several factors. Clinical manifestations of acute leukaemia are derived from the presence of hematopoiesis system by the growth of leukaemia cells, the infiltration of leukaemia cells in various organs such as liver, spleen, lymph nodes, central nervous system, kidney, testis, lung, and joint bones, gastrointestinal tract, other. The most common symptoms are fever caused by leukaemia, then pale and weak due to anemia. Manifestations of bleeding due to thrombocytopenia. Infiltration of leukaemia cells in the organ can lead to splenomegaly, hepatomegaly, and enlarged lymph nodes. Patients with acute myeloblastic leukaemia have typical symptoms of gingival hyperplasia and can be found in extramedullary infiltration. The diagnosis of acute leukaemia is based on clinical symptoms, complete blood tests and peripheral blood smear examination. The diagnosis must be established based on the study of bone marrow aspiration.

Leukaemia cutis is an aggressive leukaemia cell infiltration into the epidermal, dermis, and subcutis layers. The frequency of leukaemia cutis seems to be higher among children than adults, as many as 25–30% of infants with congenital leukaemia develop skin involvement. The incidence of leukaemic cell infiltration on the skin is infrequent, can occur in all types of leukaemia. Leukaemia cutis mostly found in AML M4 and M5 about 10-50%, while in AML M0, M1, M2, M3 to 10%.

CASE ILLUSTRATION

A boy, 12-year-old, admitted with pale approximately 10 months before admission. Pale diminish after patients receive a transfusion of red blood routine every two weeks since 3 months before admitted the hospital. He had suffered from intermittent fevers for 11 months before admission; the fever was relieved without any medication. Gum bleeding complained about 10 months prior to the admission, appearing occasionally. Swelling of the gums along with bleeding gums. Lumps on the skin for 2 months before hospital admission with a diameter of about 1 cm, solid consistency, redness, pain on the neck, face, chest, and back. The enlarged lump then bursts out pus and blood. After the rupture, other lumps appear throughout the body. Stomach enlarged for 3 months before hospital admission, swell gradually. There were no changes in bowel habits and urinary symptoms. Eating and drinking are gradually. There were no changes in bowel habits and urinary symptoms. Eating and drinking are gradually. There were no changes in bowel habits and urinary symptoms. Eating and drinking are gradually. There were no changes in bowel habits and urinary symptoms. Eating and drinking are gradually.

The patient is the eighth child of nine siblings (Figure 1), no family member who suffers from a prolonged cough, coughing up blood, is taking a drug program for 6 months, suffering from malaria, high pressure, diabetes, heart disease, stroke, kidney, asthma, convulsions, liver disease, cancer, sexually transmitted diseases, and bleeding. Brother number 5 on the month died at the age of 6 months and no known cause of death.

He was born spontaneously, rescued by shamans. There were no abnormalities seen when she was born. Immunization history is not clear. There was no delay in his developmental status. The patient was breastfed exclusively for 6 months and continued until 24 months. Patient’s daily food combination contains rice, white meat, fish, eggs, fruits, and vegetables. There was no history of allergy or a similar disease in his family.

On physical examination, the patient was alert and had a regular pulse rate, 90 beats per minute. The respiratory rate was 20 times per minute, and the axillary temperature was 36.7°C, and the blood pressure was 110/80 mmHg. His body weight was 27 kg, and the body height was 145 cm. According to 2000th CDC growth charts, the bodyweight for age charts was <3 percentile (severely underweight), the body height for age charts was 25-50 percentile (within normal limits), and the bodyweight for height was <3 percentile (severely wasted). The nutritional status was 65% (severe malnutrition).

Physical examination was obtained by gingival hyperplasia, lymph nodes were found on the right and left the submandibular region, right and left the inguinal region with a diameter of 0.5-1.5 cm. The liver was palpable 2 cm below the xiphoid process and costal arch, sharp edges, soft consistency, smooth surface, painless. The spleen was palpable at Schaffner line VI. Multiples mass in the head, neck, thorax, abdominal and hand region with a diameter of 0.5-3 cm. The clinical symptom of the patient was presented in some figures below (Figure 1).

From complete blood count, leukocyte was obtained 53.52 K/μl (neutrophil 12.98 (24.3%), lymphocyte 2.82 (5.3%)), haemoglobin 9.5 g/dl (MCV 79 fl; MCH 25.6 pg; MCHC 32.4 g/dl); haematocrit 29.5%; platelets 10 K/μl impression leukocytosis, mild anaemia, and severe thrombocytopenia. Renal function (urea 6 mg/dl, creatinine 0.26 mg/dl); electrolytes (sodium 135 mmol/L, potassium 4.35 mmol/L, chloride 100.5 mmol/L, calcium 8.68 mg/dl); liver function (ALP 57 mg/dl; total bilirubin 0.55 mg/dl; direct bilirubin 0.2 mg/dl; indirect bilirubin 0.35 mg/dl; SGOT 11.7 U/l; SGPT 4.4 U/l; total protein 5.88 g/dl; albumin 2.96 g/dl; globulin 1.96 μg/dl; gamma GT 16 U/L), uric acid 3.6 mg/dl. Blood gas analysis: pH 7.44; pO2 33; pO2 86; HCO3- 22.4. Peripheral blood smear, erythrocytes: normocytic normochromic, leucocytes: increased number, differentiation of monocytosis,
ILLUSTRATION CASE

Vacuolization (+), immature granulocytes (+), blast absent, platelets: decreased quantities, large platelets absent, conclusions: normocytic normochromic anaemia, leukocytosis, thrombocytopenia. Infection markers: procalcitonin 0.08 ng/ml.

Bone marrow aspiration cellularity: hypercellularity; erythroid system: decreased activity; myeloid system: increased activity, all myeloid series, myeloblast 10%, monoblast 5%; megakaryocytes system: decreased activity; other cells: no visible infiltration of non-haematopoetic cells in the bone marrow. Bone marrow aspiration obtained bone marrow suspicion of AML with myeloblast 10%, and monoblast 5% (Figure 3).

Skin tissue biopsy containing infiltration of diffuse blast cells with large cell morphology with a partially eosinophilic parasite of granule, spherical nucleus, fine chromatin, with prominent partial nucleotide of some other blast cells indicate cell morphology slightly larger than lymphocytes mature, moderate cytoplasm to basophilic area, round to oval nucleus, smooth granular chromatin, with multiple prominent multiple nucleotides. Seem also maturation to neutrophils. At some focal points appear granulomas with inflammatory inflammation of neutrophil PMN, lymphocytes and plasma cells. Skin biopsy gets an impressive morphological picture of cutaneous infiltration by myeloblasts and monoblasts (Figure 4).

The patient diagnosed with acute myeloblastic leukaemia, leukocytosis, leukaemia cutis, and severe malnutrition. Patients treated with hydration during hyperleukocytosis with 2000 ml/m²/day equal to IVFD D5 ½NS 2100 ml/day, adding sodium bicarbonate 25 meq in each 500 ml D5 ½ NS. Allopurinol 10 mg/kg/day equal to 100 mg every 8 hours orally. Supportive therapy to maintain optimal condition of the patient including nutritional therapy, blood component transfusion as indicated, and mucolytics. 2013 Indonesia protocol for non-lymphoblastic leukaemia with methotrexate intrathecal, vincristine, cyclophosphamide, doxorubicin, cytosine arabinose, dexamethasone, and 6-mercaptopurine. Bone marrow aspiration will be evaluated after completion of induction phase chemotherapy to assess therapy.

Food recall of patients before the illness has reached 92% based on the recommendation of dietary allowance (RDA). Nutritional requirements: maintenance fluid requirements are 1640 ml/day. Calorie requirements according to RDA are 70 kcal/kg/day equivalent to 2590 kcal/day, protein requirements are 0.9 g/kg/day equivalent to 34 g/day. Nutritional route: orally. Nutritional selection: rice and side dishes, one portion every eight hours with snacks every 12 hours. Nutritional monitoring: intake, vomiting, diarrhea, and weight gain.

DISCUSSION

Malignant diseases, infections, and autoimmune reactions in children are sometimes challenging to distinguish. Patients usually come with similar complaints of systemic symptoms such as fever, pallor, weakness, and bleeding, accompanied by disorders of organ function such as impaired consciousness, shortness of breath, enlarged abdomen, bone, and joint pain, and swollen limbs. Malignancy is often found in childhood. Acute leukaemia is 30-40% of all malignancies in childhood. Incidence averages 4-4.5 cases/year/100,000 in children younger than 15 years. Acute leukaemia has the highest incidence in children aged 2 to 6 years. The incidence is higher in whites than in blacks. In Jakarta, in 1994 the incident reached...
2,76/100,000 children aged 1-4 years. In 1996, there were 5-6 new leukaemia patients every month in Dr Sardjito Hospital Yogyakarta. Acute lymphoblastic leukaemia accounts for about 75% of all cases, acute myeloid leukaemia (AML) for about 20% and most of the remaining leukaemia are of the chronic myeloid form.4,5 Our case is a 12-year-old male; the patient came with a pale complaint for ten months, no signs of bleeding at baseline, no rash on the skin, no joint pain, no shortness of breath. In physical examination, no rapid pulse was obtained, enlarged lymph nodes in retroauricular and inguinal regions, multiple nodules, gingival hyperplasia, and splenomegaly. From the clinical symptoms of the patient more suspected of acute leukaemia.

The cause of leukaemia is not known with certainty, allegedly associated with several factors, including: genetic factors (monozygotic twins, Trisomy 21), parental factors include the age of the parents when pregnant, history of previous miscarriage, birth order; preconception and prenatal exposures include alcohols, cigarettes, drugs (sulfa, alkylating agents, topoisomerase inhibitors), chemicals such as pesticides, exposure to electromagnetic fields such as residence in high-voltage electrical lines, ionizing radiation; exposure to x-rays during pregnancy, and child factors include low birth weight and duration of breastfeeding.4,6

Clinical manifestations of acute leukaemia are derived from the presence of hematopoiesis system by the growth of leukaemia cells, the infiltration of leukaemia cells in various organs such as liver, spleen, lymph nodes, central nervous system, kidney, testis, lung, and joint bones, gastrointestinal tract, other. The most common symptoms are fever caused by leukaemia, then pale and weak due to anaemia. Manifestations of bleeding due to thrombocytopenia.3 Infiltration of leukaemia cells in the organ can lead to splenomegaly, hepatomegaly, and enlarged lymph nodes. Patients with acute myeloblastic leukaemia have typical symptoms of gingival hyperplasia and can be found in extramedullary infiltration.4 Our case came with a pale and fever for 10 months before admission and was accompanied by red patches and bruising on the skin when the patient was hospitalized. He also complained of gingival hyperplasia, splenomegaly and multiple nodules in scattered skin that are appropriate for clinical acute myeloblastic leukaemia (AML).

The diagnosis of acute leukaemia is based on clinical symptoms, complete blood tests and peripheral blood smear examination. The diagnosis must be established based on the study of bone marrow aspiration. In the bone marrow, there is normally a blast cell <5%. The diagnosis of leukaemia is confirmed when a blast cell in the bone marrow is > 25%.7,8,9 According to the French American British Group (FAB) classification, AML is divided into seven, ie M0 (acute myelocytic leukaemia with minimal differentiation), M1 (myelocytic leukaemia without maturation ), M3 (hyper granular promyelocytic leukaemia), M4 (acute myelomonocytic leukaemia), M5 (acute monocytic leukaemia), M6 (erythroblastic leukaemia/ erythroleukaemia), and M7 (acute megakaryocytic leukaemia).4,6,8
Our case, routine blood results show normocytic normochromic anaemia and thrombocytopenia. Bone marrow aspiration showed infiltration of myeloblast cells of about 10% and monoblast 5%. Based on clinical manifestations and investigations, the patient is diagnosed with AML.

Acute myeloid leukaemia is a bone marrow disease, and leukaemic infiltration of other organs (extramedullary leukaemia, EML) is a relatively rare, but interesting phenomenon. The diagnosis of an extramedullary illness is also clinically crucial since EML may adversely affect prognosis and particular therapeutic strategies may be required. EML may occur without bone marrow involvement (primary EML) but usually becomes clinically evident in close temporal relationship with overt leukaemia. The site of EML may be the central nervous system, skin, ovary, orbital, gums, lymph nodes, and a variety of other organs. The reason why some patients with AML have EML is unclear, but it has been shown that patients with higher white blood cell counts French-American-British (FAB) M4 and M5 subtypes, t(8;21), inv.16, and t(9;11) have a higher incidence of EML.8,9

Leukaemia cutis is defined as cutaneous infiltration by neoplastic leucocytes (myeloid or lymphoid), resulting in clinically identifiable cutaneous lesions. Although the general symptoms and cutaneous features of various leukaemias and lymphomas often tend to resemble one another, each will frequently have its own characteristic appearance and distribution. When composed of neoplastic granulocytic precursors, leukaemia cutis has been designated as myeloid sarcoma, granulocytic sarcoma, primary extramedullary leukaemia or chloroma. When composed of neoplastic monocytic precursors (monoblasts and promonocytes), leukaemia cutis also has been designated as monocytic sarcoma. The terms myeloid sarcoma and extramedullary myeloid cell tumour have also been used to include both granulocytic and monocytic tumours.2,9,10

Leukaemia cutis is an aggressive leukaemia cell infiltration into the epidermal, dermis, and subcutis layers. The frequency ranges from 3% to 30% depending on the type of leukaemia and seems to be higher among children than adults, as many as 25–30% of infants with congenital leukaemia develop skin involvement.8,11,12 The incidence of leukaemic cell infiltration on the skin is infrequent, can occur in all types of leukaemia. Leukaemia cutis mostly found in AML M4 and M5 about 10-50%, while in AML M0, M1, M2, M3 to 10%. No data on leukaemia cutis related to a specific race, sex, and age. Classification of leukaemia cutis can be both specific and non-specific (leukemoid) lesions. The features of skin lesions vary, generally appearing as macules, papules and multiple nodules, 1-2.5 cm in diameter, firmly defined, palpable as solid, supple, no itchy and painless. Sometimes plaques, ulcers, bullae and somewhat rare as palpal purpura and may occur as single or generalized lesions. In AML M5 lesions tend to be large and purplish, the skin thickens mainly on the face. While in AML M4 are nodules (70%), papules (52%), ecchymoses (26%), placards (22%), purpura (17%), macules (13%). Leukaemia cutis has no specific predilection; the same distribution over the whole body can be a single lesion or spread to 70% of the body surface. In 50% of cases, AML M4 and M5 are common gingival hypertrophy as a result of leukaemia infiltration.2,9,11

Leukaemia cutis is a local manifestation of an underlying systemic process; therefore, treatment should be directed at eradicating the leukemic clone by using systemic chemotherapy. Treatment should be tailored according to AML subtype and by the patient’s ability to tolerate the treatment. Leukaemia cutis is uncommon as the presenting feature of AML and is associated with an unfavourable prognosis.2,12,13 In our case, a purplish red nodule is found in the head, neck, thorax, abdominal and hand region corresponding to the leukaemia cutis image. A skin biopsy was performed on this patient, and a cutaneous infiltration result was obtained by myeloblast and monoblast.

Hyperleukocytosis is defined as the number of peripheral blood leucocytes that exceed 100,000/μl. It is found in 9-13% of children with acute lymphoblastic leukaemia (ALL), in 5-22% of children with acute non-lymphoblastic leukaemia and in almost all children with chronic myelocytic leukaemia (CML) chronic phase. Hyperleukocytosis can lead to leukostasis syndrome, a syndrome caused by a small arterial blockage by aggregate/blast cell thrombi. Patients with myeloblastic leukaemia are more likely to develop this syndrome than patients with lymphoblastic leukaemia. This is due to the higher volume of myeloblast cells (350-450 mm3) compared with the number of lymphoblast cells (250-350 mm3), in addition to the more rigid properties of myeloblast cells. The management of hyperleukocytosis is hydration, leukapheresis or chemotherapy as soon as possible after diagnosis.13,14 To determine the effectiveness of chemotherapy as a treatment option of hyperleukocytosis, we found an evidence-based journal "Minimally early morbidity in children with acute myeloid leukaemia and hyperleukocytosis treated with prompt chemotherapy without leukapheresis" by Chen et al.15 in the Journal of Formosan Medical Association 2014. This journal is valid, important, and applicable (level of evidence 1b, grade of recommendation A). This study concluded...
that hyperleukocytosis therapy in patients with acute myeloblastic leukaemia using chemotherapy according to the protocol, is more effective than leukapheresis. Our case has done the hydration effort to decrease the leukocyte level, but after five days of hydration treatment there is no decrease of leukocyte count after which chemotherapy is done immediately according to non-lymphoblastic acute leukaemia protocol.

Management of leukaemia includes curative and supportive therapy. Curative therapy aims to cure leukaemia, a form of chemotherapy that includes the induction phase, consolidation, intensification, central nervous system prophylaxis, and maintenance. The treatment protocol used is the 2013 Indonesia protocol for non-lymphoblastic leukaemia with methotrexate intrathecal, vincristine, cyclophosphamide, doxorubicin, cytosine arabinose, dexamethasone, and 6-mercaptopurine. The conditions of chemotherapy include haemoglobin ≥10 mg/dl, leukocyte level <50 K/ul, thrombocyte level 30-50 K/ul, serum creatinine within normal limits and transaminase enzyme levels not exceeding four times the upper limit of normal.1,8,16 Supportive therapy includes the treatment of other diseases that accompany leukaemia and treatment of complications such as blood transfusion, antibiotic or antifungal therapy as indicated, good nutrition and psychosocial aspects approach.1,17 Our case is acquired with anaemia, thrombocytopenia, so a packed red cell (PRC) and thrombocyte concentrate (TC) transfusion are done for the preparation of chemotherapy.

Malnutrition in malignancy diseases better known as cancer cachexia has different pathophysiology with classic protein-energy malnutrition caused by lack of food. Cancer cachexia is a complex syndrome characterized by progressive weight loss associated with anorexia, asthenia, anaemia and immunologic function changes. Broadly speaking, the occurrence of cancer cachexia caused three factors, namely physiological, metabolic and psychological factors. Anorexia and metabolic disturbance in cancer cachexia as a result of interaction between tumour and host. The initial response to malignant male hostility results in the immune response of cytokines (TNFα, IL-1β, IL-6, and INFγ) in an attempt to kill tumour cells. If an inadequate hostess and/or rapid tumor growth, the ongoing production of cytokines will have a negative effect of anorexia and changes in the metabolism of proteins, carbohydrates, and lipids. Nutritional status of patients with malignancy is also known to have a relationship with the outcome of the patient. Patients with malnutrition have a poorer prognosis and outcomes than children with good nutritional status.18,19,22 Surveys have found that dietary intervention is not incorporated routinely into supportive care regimens. Nutritional depletion has been associated with poorer outcomes, increased abandonment of therapy, and treatment-related toxicities.20 We conducted a journal search and obtained a journal entitled “Clinical implication of malnutrition in child cancer patient-infection and mortality” by Loeffen et al. in Support Care Cancer 2015 (level of evidence 2b, grade of recommendation B).21 The journal concludes that subjects with malnutrition at the start of the diagnosis had a worse life expectancy rate than children with proper nutrition. Our case with acute myeloblastic leukaemia with malnutrition type marasmus has a worse life expectancy.

The prognosis of AML patients is divided into three groups based on clinical and laboratory findings that are favourable, intermediate, and unfavourable. The prognosis of AML patients is affected by patient age, a number of chromosomal abnormalities, infiltration of multifor-mat cells, leukocyte level, response to induction chemotherapy, multidrug therapy resistance, extramedullary leukaemia, and secondary leukaemia.1,3,6 In younger patients, complete remission (CR) rates of ³80% may be reached.19 The survival rate until 2-year ahead for the favourable prognostic group is 50-85%, the intermediate prognosis group is 40-50% and the unfavourable prognostic group it is 10-20%. Extramedullary infiltration is also suspected to be a prognostic factor in children with acute myeloblastic leukaemia.8 The involvement of central nervous system and extramedullary infiltration with leukocytosis >100 x 10⁹/L at the time of diagnosis has a high risk of relapses, and a further treatment approach is required in this group of patients.22 A study by Kaddu et al.23 showed an average survival time in AML to be 7.5 months and in CML, 9.4 months. Another study by Baer et al. revealed that of 18 patients with leukaemia cutis in AML, 90% had other sites of extramedullary involvement, and, in 40% of these patients, the meninges were involved.8 In a smaller case series by Shaikh et al. with only 5 patients with AML, all 5 died within 6 months of their diagnosis of leukaemia cutis.24

After 4 months of chemotherapy, patients and families decided not to continue chemotherapy and only doing supportive therapy such as transfusions. The patient passed away 9 months after the diagnosis.

CONCLUSION
Leukaemia cutis is uncommon as the presenting feature of AML and is associated with an unfavourable prognosis. There is no specific treatment for cutaneous leukaemia other than palliation and
symptomatic relief. The 2-year survival rate for the unfavorable prognostic group it is 10-20%.

REFERENCES


