Leukaemia Cutis (LC) Involvement Revealing Chronic Myeloid Leukaemia (CML) Relapse: A Case Report

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Abstract

Leukaemia Cutis (LC) is a skin infiltration which takes place via neoplastic leukocytes. Its frequency is usually dependent on the diagnosis of primary leukaemia. It is commonly observed in acute myeloid leukaemia (AML). However, it is also rarely observed in case of chronic myeloid leukaemia (CML). Thus, for present report, a case of a patient with LC involvement, presenting MLC is considered. A 62-year-old male patient with a past history of MCL was presented to haemato-oncology department in a hospital located in Beijing, China, with painful hematoma as well as subcutaneous nodes. Laboratory, coagulation, and histopathology investigations presented thrombocytosis, leucocytosis, dissemination of intravascular coagulation, anaemia, and elevation of inflammatory markers. Aspiration of bone marrow also showed proliferation of granular lineage without any excessive blasts. This presented the option of recurrence of CML or AML progression. Moroever, skin biopsy also helped in confirming LC, presenting the myeloid-like cells' hypodermal and dermal infiltration, without transforming AML. The immunochemistry implemented in this case, also supported the LC diagnosis. The patient was also treated with Dasatinib which also contributed to MCL recurrence. Thus, LC is stated as a rare manifestation of CML, especially outside the bone marrow of the patient. LC involvement is a rare manifestation of CML relapse. However, in present case, the presence of subcutaneous nodes on the buttock, knee, and forearms of the patient, helped in diagnosing MCL recurrence.

Keywords: Leukaemia Cutis, Relapse, Chronic Myeloid Leukaemia, Histology, Dasatinib.

Background

Leukaemia cutis (LC) is referred as a skin infiltration which is demonstrated clinically. It takes place through neoplastic leukocytes or associated precursors within the dermis, subcutaneous or epidermis tissues. It is a rare symptom which is observed within disease's advanced stage. LC frequency ranges from 2 to 30%, based on the primary leukaemia diagnosis.[1] LC may occur at the same time or follow systemic leukaemia. However, LC is often diagnosed as leukaemia's primary manifestation. Different subtypes of leukaemia are found to cause skin infiltration. Moroever, LC is commonly observed within the context of children who suffer from congenital leukaemia. It is usually observed in 25 to 30% of such cases.[1] However, the highest LC incidence has been observed within the context of "acute myeloid leukaemia (AML) of myelomonocytic and monocytic FAB ("French, American, British") subtypes, chronic lymphocytic leukaemia (CLL), T-cell leukaemia's and chronic lymphocytic leukaemia (CLL). It has also been observed with "chronic myeloid leukaemia (CML) or myelodysplastic syndrome." LC often present an indication of advanced disease, incorporating additional extramedullary sites.[2] This is often related to poor prognosis.

Moreover, LC is found to correlate with leukaemia progression and is also concomitant within a large majority of related extramedullary involvement. It may also be diagnosed before the onset of haematological disease and is stated as aleukemia LC. Therefore, etiopathogenesis behind the migration of skin neoplastic leukocyte still remains unclear. However, the mechanism including chemotaxis have been clearly, focusing on the "skin selective homing" concept.[3] In general, LC is found to be asymptomatic, whereas most of the time, LC is presented as small bumps present on the skin, which are also known as papules. However, sometimes, larger bumps which are also known as nodules, appear. These bumps are not painful, and

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they are usually purple or red in colour. The colour of these bumps can be similar to the skin colour. In addition, individuals with AML may also suffer from profuse bleeding, which can result in bruising. The lesions of LC usually appear on legs, but they can also be found on the scalp, trunk, face, and arms. Therefore, individuals with AML, who so not suffer from LC, have a survival rate of 30% at 2 years, whereas, it reduces to 6% among the individuals with lesions on their skin.[4] Thus, the individuals with LC and AML usually need aggressive treatment. However, individuals with CLL, are found to have a survival rate of 83% at 5 years. This outlook does not change even with the presence of lesions.

Moroever, the incidence rate of leukaemia is also found to be increasing in different developing and developed countries. For instance, in China its incidence rate was found to be 6.65/ 100,000 among males and 5.8/ 100,000 among females.[5] Over the years, different treatments have been introduced for leukaemia. The most commonly used treatment for leukaemia includes chemotherapy. However, other options can also be considered, based on the age, health of the individual and the leukaemia type. Another treatment method that is applied for treating leukaemia include radiation therapy. External beam radiation is considered to be typical type of treatment which is used for blood cancers. In this therapy, a radiation beam is delivered via various angles from outside of the body.[6] The main aim of this beam is to damage the DNA within the cancer cells. This process is considered to be effective in stopping the growth of the cells. Another therapy which can be considered for treating leukaemia, includes immunotherapy. It is referred as a biological therapy in which the immune system of the body is used for fighting against the cancer. It is administered via an injection that enhances activity of cells of immune system or blocks the cancer cells' signals (which can reduce the immune response). This type of therapy can also be given via intravesical, topical or oral route. Another method which is used for the treatment of leukaemia includes transplantation of stem cells. It is also referred as bone marrow transplant. Via this treatment, stem cells which are damaged by the cancer or radiation therapy or other associated chemotherapy, are replaced by healthy stem cells. It has also been crucial for treating LC lesions in order to treat leukaemia. As a result, different important treatments have also been introduced for treating LC. Different treatments that can be used for this purpose, include localised therapy in which light therapy or electron beam is used for reducing skin lesions.[7] In this regard, topical treatments, including lidocaine, steroid creams as well as other medications can also be used for overcoming pain as well as other symptoms. Moreover, other antimicrobial medications are also used for preventing related infections that might enter the individual's body via skin lesions.[8] The time length within the context of LC lesions depended on different factors, such as response of the leukaemia to different treatments. Therefore, with efficient treatment, the fading of lesions is observed. In this regard, other factors such as age as well as overall health of the individuals can also impact the spreading of lesions. Even though different treatments have been introduced over the years for treating leukaemia, still it persists as a challenging disease to live with. Therefore, for this report, a case of LC presenting a CML relapse, is considered for a 62-year-old individual within the context of China. This patient is treated with Dasatinib (it is an oral anticancer drug which used as a targeted therapy for treating particular types of bone marrow or blood cancers. It is also categorised as a "BCR-ABL tyrosine kinase inhibitor (TKI)"). This drug is most commonly used for treating Philadelphia chromosome which is positive CML (Ph + CML). It is usually used in adults after other treatments such as imatinib, do not work.

Case Report

A 62-year-old male patient was administered to the haemato-oncology department in a hospital located in Beijing, China. He was complaining about multiple subcutaneous nodes, present on his left buttock, knee, and forearms. These nodes were firm and painful. He initially described the associated nodes which were followed by hematoma, surrounding them. In this regard, the past medical history of the patient was also noted. Therefore, the past medical history of the patient showed his treatment with amlodipine for arterial hypertension. The patient also had a medical history of CML. The patient was diagnosed with CML in the years 2008 and was treated with Imatinib (a blocker, also stated as TKI, used for inhibiting cancer growth) in the initial three years. The therapeutic response of the patient to this drug was inadequate. Later on, Dasatinib was prescribed to the patient which was also controlled partially. The patient also complained regarding the worsening arthralgia, sub-pyrexia, and dyspnea. However, no history regarding the travel, trauma, initiation of new drug or infection was provided. Furthermore, the patient acknowledged irregular intake of medication. Moroever, the patient was not found to be febrile during physical examination. Unremarkable chest auscultation was observed within the context of the patient, showing significant findings. At the same time, rheumatological examination was also done which showed that no joint effusion was present. As a result, the joints of the patient were not swollen. Skin examination of the patient was also done. The results obtained from this examination, presented firm as well as painful subcutaneous nodes on the forearms, knee and buttock of the patient. These nodes had peripheral hematoma and purplish discoloration at its circumference. Figure 1 shows the purplish discoloured subcutaneous nodes along with peripheral hematoma, observed on the forearms of the patient.

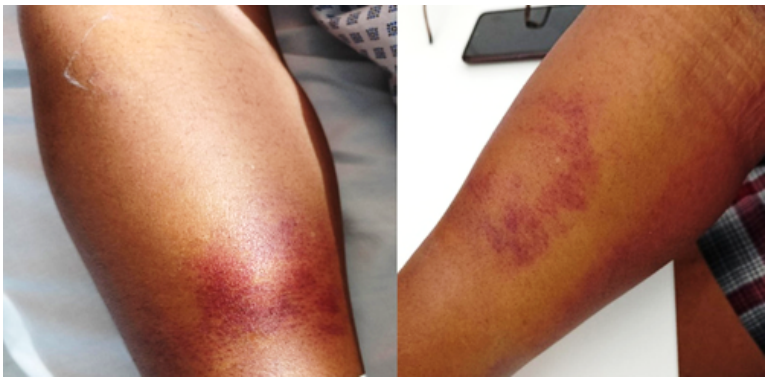

Figure 1: Purplish Discoloured Subcutaneous Nodes, Along with Peripheral Hematoma on the Forearms of the Patient.

At this stage, the results obtained from the skin examination were considered and the skin features were focused on detail, especially within the context of CML. Different diagnoses were made. The most accurate of these diagnoses include: (a) erythema nodosum, (b) LC, (c) nodular hypodermitis and (d) cutaneous vasculitis.
Laboratory tests were also conducted to attain the required findings. Table 1 shows the obtained findings of these tests.

Table 1: Laboratory Tests Findings of the Patient.

Parameter	Normal Range	Obtained Result
Haemoglobin level	13 to 17 g/dL	9.5 g/dL
White blood cells (WBCs) count	3.5 to 11 $\times 10^9$ / L	199.34 $\times 10^9$ / L
Neutrophils count	1.5 to 6.7 $\times 10^9$/L	93.06 $\times 10^9$ / L
Lymphocytes count	1 to 4 $\times 10^9$ / L	7.17 $\times 10^9$ / L
Monocytes count	0.2 to 0.8 $\times 10^9$ / L	24.3 $\times 10^9$ / L
Platelets count	150 to 400 $\times 10^9$ / L	389 $\times 10^9$ / L
C-reactive protein	< 5 mg/ L	18.7 mg/ L
Haptoglobin	50 to 220 mg/ dL	< 10 mg/ dL
Creatinine	0.8 to 1.3 mg/ dL	1.33 mg/ dL
Lactate dehydrogenase	50 to 150 U/ L	7.268 U/ L
Uric acid	3.5 to 7.2 mg/ dL	12.4 mg/ dL

The laboratory tests obtained for the patient showed that the haemoglobin level was below the normal range, while the count of WBCs, neutrophils, lymphocytes, monocytes, and platelet counts were found to be higher than their normal range. The value of C-reactive protein was more than the normal range. Within these tests, 5% of the blasts were also observed. Moreover, the haptoglobin level was less than the normal value and the creatinine level was higher. However, the level of lactate dehydrogenase was less than the normal range and the uric acid level was found to be higher.
Additionally, coagulation tests were also conducted which were in association with a "disseminate intravascular coagulation (DIVC)." Table 2 shows the results of these tests.

Table 2: Coagulation Test Results.

Parameter	Normal Range	Obtained Result
D-dimer	< 500 ng/ mL	23.076 ng/ mL
Fibrinogen	1.8 to 4 g/ L	1.08 g/ L
Prothrombin ratio	85 to 100%	40%

The results obtained from the coagulation tests showed that the value of D-dimer was in range, while the fibrinogen level was less than the normal range and the prothrombin ratio was also found to be lower. Moreover, the blood haemocultures were insignificant.
Moreover, the serological assays conducted within the context of patient for syphilis, Rickettsia, HCV, and HIV were found to be insignificant, whereas, immunological scar was presented with EBV, HBV and CMV. Suspicion regarding CML reoccurrence was raised due to leucocytosis. This has also raised the concerns regarding AML progression.
A rich marrow was demonstrated by the bone marrow, with granular lineage proliferation. In this regard, no excess blasts were observed (3.8%) and was found to be linked with dysplasia on the megakaryocytic as well as erythroid lineages (OGATA score was found to be 2/ 4). Moreover, the biopsy of skin of left knee also presented a moderate derma interstitial infiltrate as well as hypoderm, incorporating myeloid-like cells at different maturation stages without excess of blasts. Figures 2 and 3 present the histopathology findings in this regard. In addition,

the immunohistochemistry analysis of the patient also presented a strong significant reaction against "anti-MPO antibody." No staining was observed against $CD117^+$ and $CD34^+$. At the same time, the basal membrane, stratum cornuem and epidermis were found to be unaffected. The histological appearance was found to be consistent with a hypodermal, dermal and LC infiltration of the associated CML cells, without getting transformed into AML.

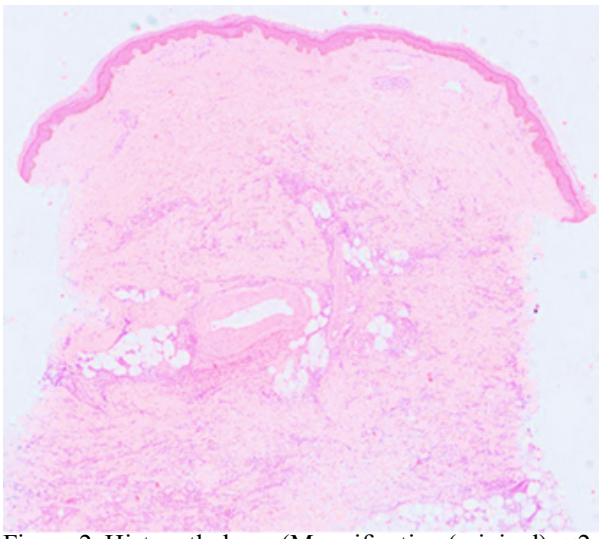

Figure 2: Histopathology. (Magnification (original)- ×2, 5). The Histological Examination of Stratum Corneum, Basal Membrane and Epidermal Layer was Found to be Unremarkable. The Sites of Hypodermis and Dermis Presented Positive Interstitial Infiltration.

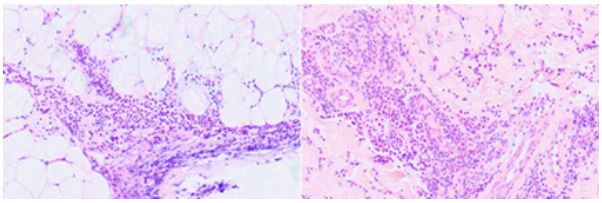

Figure 3: Histopathology. (Magnification (original)- ×2, 5). Hypodermis and Dermis Interstitial Infiltrate by MLC without Excess of Blasts.

The final diagnosis within the context of current patient showed a CML relapse which was presented by LC. It was also complicated due to the interruption of Dasatinib and DIVC. At this time, Hydrea was used for treating the patient before he returned to Dasatinib. The patient's haematological follow-up was also marked by clinical as well as biological CML remission with LC's complete regression.

Discussion

In the present case, the patient has gone through a CML relapse which has been presented by the involvement of LC. These lesions are commonly observed within the adults, especially within the case of CML. However, LC appearance is usually linked to the transformation within a blastic phase, showing the associated disease progression.[3] This was not observed in the current case. Therefore, within the current case, no additive bone marrow's infestations (incorporating the insufficiency of bone marrow, associated with cytopenia) were observed. These may be interpreted rigorously. The involvement of other related extramedullary may be presented within a patient with LC (taken as central nervous system).[9] This can make the prognosis worst. However, this was not observed in current case. Another feature which presents the involvement of extramedullary includes the osteoarticular pain. The patient in the current case also complained about this pain. However, in this case, swelling of the joint has to be differentiated from the crystal arthropathies, providing a natural tendency to formulate gout, within the context of active leukaemia. However, the reports obtained for the patient within the present case scenario, showed the occurrence of LC within the patient who has been diagnosed with CML. In this case, no progression was observed to the blast phase and no involvement of extramedullary was observed, instead of associate cutaneous manifestation. Furthermore, LC is found to occur in different forms which include plaques, nodules, and papules. These lesions are most commonly observed in the form of purplish discoloured nodes, which have also been observed in the current case.

However, differential diagnosis of such manifestations is found to be broader, incorporating inflammatory, chemotherapy-related and neoplastic conditions (such as neutrophilic dermatosis, erythema nodosum and other related conditions).[10] It might also include different infections, which take place due to immunosuppression. Therefore, emphasis has been given on histology in order to diagnose the associated condition. LC diagnosis depends on histopathology, specifically tissue immunophenotyping as well as immunohistochemistry. However, in present case, cutaneous involvement was found to be localized within the subcutaneous and dermis tissue. It is also characterized by positive MLC interstitial infiltrate ate different sites, without the incorporation of excessive blasts. Further laboratory tests and coagulation tests performed within the current case also helped in confirming LC diagnosis, presenting an enhanced anti-MPO staining expression. This is found to be persistent with the already present literature.[11] It has also been observed that skin biopsy alone cannot be relied upon, for categorizing different leukaemia forms. As a result, emphasis has been given on further investigations, including molecular genetics and cytochemical analyses. Moroever, if suspicions are raised regarding LC, then biological assessment can be conducted along with the aspiration of bone marrow as well as osteo-medullar biopsy. This helps in developing systemic leukaemia diagnosis. In the current case, the lack of therapeutic observance was also present. Therefore, LC's therapeutic approach depends on the malignant hemopathy's management treatment. It varies in association with the extramedullary involvement's nature. However, if chemotherapy is contradicted within the context of LC, then only radiotherapy can be utilised symptomatically to

overcome the pain as well as pruritus which are induced by the LC.[12] However, a combination of chemotherapy and radiotherapy does not result in adding additional treatment improvement. However, within the current case, Dsatinib interruption was also found to contribute to CML relapse. Thus, the patient can be recommended effective chemotherapy or radiotherapy in order to treat the associated LC.

Conclusion

LC's clinical presentation is polymorphic, and it can also be effective in revealing a malignant hemopathy. Even though, LC is commonly described within the context of AML, however, it is also observed in case of CML. LC is stated as a rare type of malignant hemopathy's extramedullary feature which is also related with CML. The clinical presentation of LC is found to be pleiotropic, whereas its differential diagnosis is broader. It depends on typical histological, clinical as well as biomolecular concordance. Therefore, when LC is confirmed, its treatment is dependent on its primary condition. For this purpose, a case of LC has been presented which reveals a CML relapse. For this purpose, different laboratory as well as coagulation tests were conducted. The histopathology was found to be most effective within the context of diagnosis of LC. However, the CML relapse within the context of current case was found to be treated by TKI successfully.

In conclusion, leukaemia cutis is malignant hemopathies' rare manifestation. It is rarer within the context of CML. The diagnosis of this condition depends on clinical suspicion and different diagnosis techniques are required for confirming it. These techniques include molecular, histological, and biological investigations, especially within the context of malignant hemopathy. The diagnosis of LC is also found to be crucial in determining the CML relapse.

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