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Cytodiagnosis of Extramedullary Leukemic Infiltration: A series of Nine Cases

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ABSTRACT

Nine cases of extramedullary leukemic infiltration were examined using fine-needle aspiration cytology (FNAC), focusing on clinical presentations, cytological findings, and hematological diagnoses. The cases included chronic myeloid leukemia (CML) and acute leukemia, with extramedullary sites such as lymph nodes, skin, pleural fluid, and soft tissue affected. FNAC smears commonly showed scattered granulocytic precursor cells, blasts, and mature neutrophils. One case presented with malignant pleural effusion. The cytological features helped distinguish leukemic infiltration from lymphoma, although challenges arose when FNAC was used without considering the full hematological context. The study concluded that extramedullary leukemic infiltration can occur at various stages and locations, and FNAC is an effective diagnostic tool when combined with peripheral smear examination and patient history. This emphasizes the importance of comprehensive monitoring and interdisciplinary collaboration for accurate diagnosis and treatment planning in these cases.

1. Introduction

Patients with leukemia may experience extramedullary involvement at any point in disease progression, whether during its course, preceding marrow leukemia onset, or during relapse. Extramedullary deposits may be a presenting feature of acute myeloid leukemia (AML)[1] and may be observed in approximately 10% of patients with chronic myeloid leukemia (CML).[2] Involvement of the liver, spleen, musculoskeletal system, head, and neck has been reported previously.[3] Pleural effusion in acute leukemia is rare.[4] Leukemic lymph node (LN) infiltration is uncommon. Clinically, it may mimic lymphoma, metastatic tumors, or infectious ailments.[5] Fine-needle aspiration cytology (FNAC) provides good morphological details of the blasts and other granulocytic cells. Therefore, it can aid in the diagnosis and planning of leukemia. This series of nine cases delves into the cytological characteristics of leukemic infiltration aspirates and briefly reviews the literature.

2. Case presentation

Case 1

A 28-year-old male presented with abdominal pain, and lymph node swellings in the inguinal region were noted, with the largest lymph node measuring approximately 1 cm. FNAC smears were cellular and showed predominantly scattered granulocytic precursor cells, ranging from the blast population to myelocytes, metamyelocytes, and mature neutrophils. Blasts with increased N: C ratio, prominent nucleoli, and scant cytoplasm were seen against the background of lymphoreticular cells, lymphocytes, and red blood cells (RBCs). A cytological diagnosis of leukemic infiltration was made. A hematological diagnosis of chronic-phase CML was made.

Case 2

A 38-year-old woman with a history of chronic phase CML presented with vomiting, generalized weakness, and painful swelling on the left thigh measuring 2x1.5 cm. FNAC smears of the swelling were cellular and showed scattered granulocytic precursor cells, including blasts, myelocytes, metamyelocytes, and mature neutrophils. Few eosinophils were present against the background of RBCs. These findings indicated myeloid leukemic infiltration.

Case 3

A 70-year-old male presented with decreased appetite, weight loss, and bilateral inguinal lymph node enlargement, with the largest measuring approximately 1.5 cm. FNAC smears revealed good cellularity and the presence of myeloid series cells, including myeloblasts, metamyelocytes, band forms, and neutrophils. Numerous eosinophil lymphoid cells and immature erythroid cells were present against the background of RBCs. Extramedullary hematopoiesis was the cytological impression. A complete blood count and peripheral blood film revealed a diagnosis of CML (chronic phase).

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Case 4

A 60-year-old male with a history of cough, shortness of breath, foot swelling, and bilateral inguinal lymphadenopathy underwent FNAC of the largest inguinal lymph node measuring approximately 2 cm. Leukemic infiltration and chronic phase CML were the cytological and hematological diagnoses, respectively.

Case 5

A 6-year-old girl presented with abdominal pain, distension, decreased appetite, and shortness of breath. Pleural effusion and generalized lymphadenopathy (largest inguinal lymph node, approximately 1.5 cm in size) were found on clinical examination. The pleural fluid was reddish-hazy in appearance. The centrifuged pleural fluid sample smear was cellular and showed malignant cells predominantly scattered singly. Malignant cells were small to medium in size with a high N: C ratio, irregular nuclear membrane, open chromatin, inconspicuous nucleoli, and scant cytoplasm against hemorrhage against the background containing many degenerated cells and lymphocytes. Cytological features indicated malignant pleural effusion (Indian Academy of Cytologists category-5) (Fig. 1A). On peripheral blood film examination, a diagnosis of acute leukemia (Fig. 1B) was made and confirmed by flow cytometry.

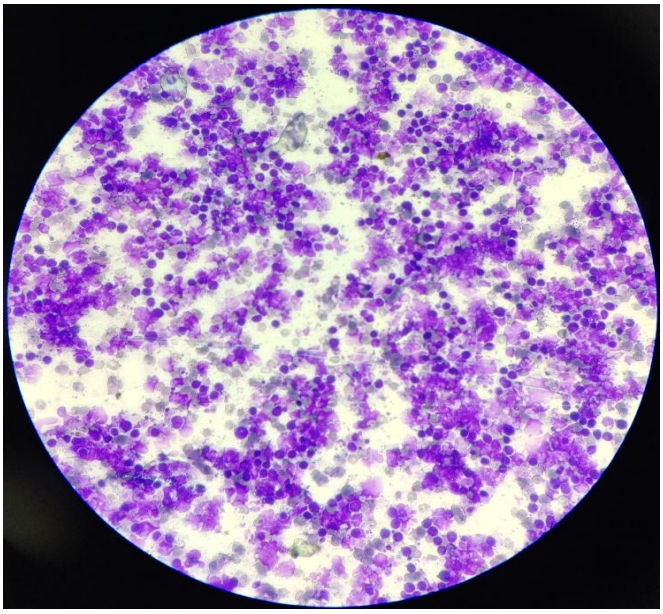

Fig. 1A. Cytospin-processed smear of pleural fluid revealing uniformly dispersed haematolymphoid blasts and few mature lymphocytes (Field stain, 40X).

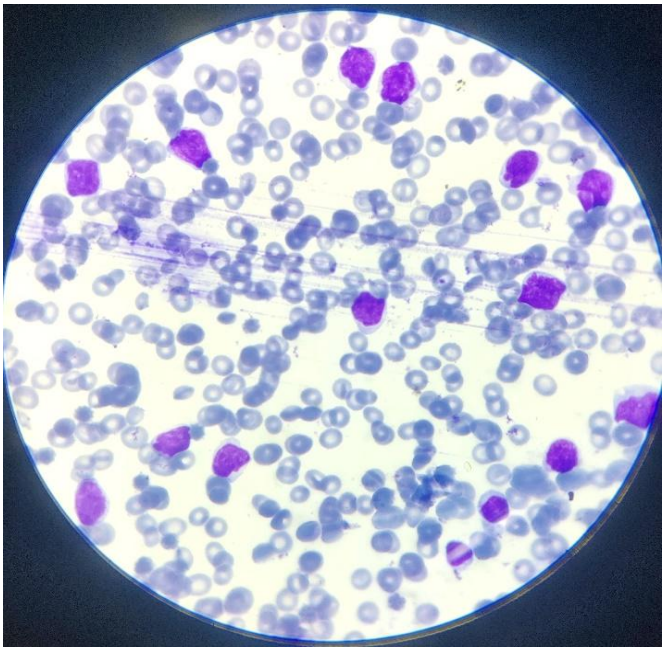

Fig. 1B. Peripheral blood smear showing medium to large-sized blasts. The nuclei are variable in shape and contain 1-2 nucleoli with clumped chromatin and irregular nuclear membrane, suggestive of a diagnosis of acute leukemia (MGG stain, 100X).

Case 6

A 53-year-old woman with a history of fever, reduced appetite, and weight loss underwent FNAC of a right supraclavicular lymph node approximately 1 cm in size. The smears were cellular and showed the presence of malignant lymphoid cells. Malignant cells were medium to large with a high N: C ratio, pleomorphic nuclei, irregular nuclear membranes, and granular chromatin with a small cytoplasm. Many cells showed atypical mitotic figures against the background of lymphoglandular bodies and RBCs. Non-Hodgkin's lymphoma was diagnosed based on these cytological findings. A complete blood count and peripheral blood film revealed acute leukemia.

Case 7

A 33-year-old man with a history of fever, weight loss, and abdominal pain presented with multiple enlarged cervical lymph nodes (approximately 1 cm). FNAC smears were cellular and showed scattered granulocytic precursor cells, including blasts, myelocytes, metamyelocytes, and mature neutrophils, against the background of RBCs. Peripheral blood film examination revealed a diagnosis of CML (chronic phase).

Case 8

A 45-year-old woman presented with purpuric lesions all over the body after complete remission of CML. FNAC smears from purpuric lesions were cellular and showed scattered granulocytic precursor cells, including blasts, myelocytes, metamyelocytes, and mature neutrophils. Few eosinophils against the background of RBCs. Cytological features indicated leukemic infiltration (leukemia cutis).

Case 9

A 46-year-old woman presented with a fever, weight loss, and right-sided cervical lymphadenopathy. FNAC smears revealed scattered granulocytic precursor cells, including blasts, myelocytes, metamyelocytes, and mature neutrophils, against a background of lymphoreticular bodies, lymphocytes, and RBCs. The cytological findings indicated leukemic infiltration (Fig. 2A). Peripheral blood film examination revealed a diagnosis of chronic-phase CML (chronic phase) (Fig. 2B), which was confirmed using the BCR-ABL1 fusion gene study. Table 1 provides a summary of the cases.

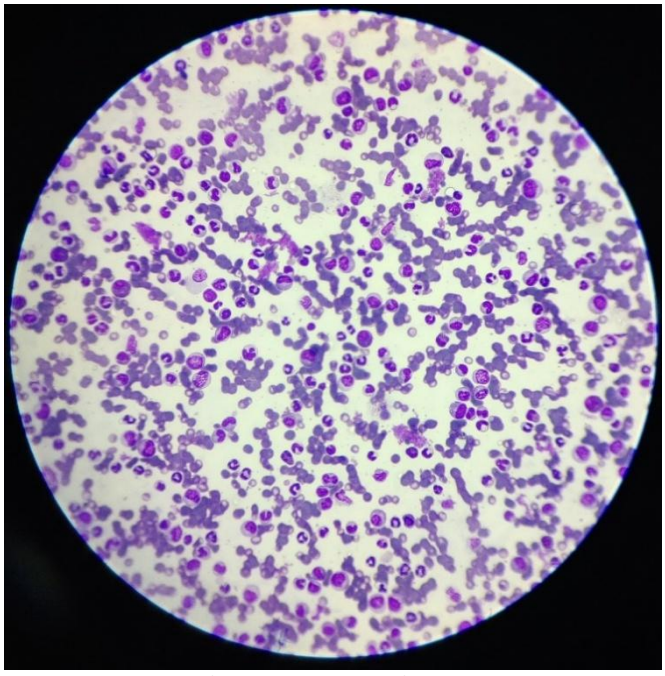

Fig. 2A. FNAC of cervical lymph node from CML patient revealing many myelocytes and metamyelocytes (Fields stain, 40X).

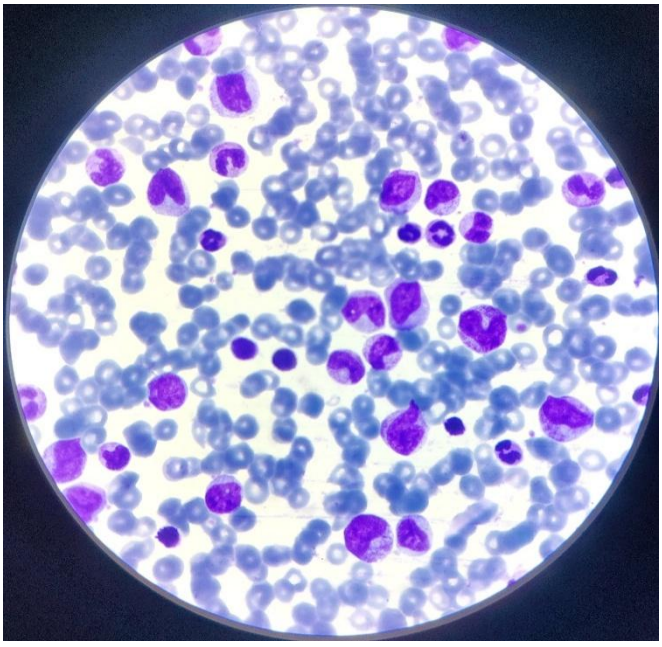

Fig. 2B. Peripheral blood smear showing all stages of myeloid cells from blast cell to neutrophils consistent with diagnosis of Chronic myeloid leukemia (MGG stain, 100X).

Table 1. Overview of the clinical findings of the cases.

Case Number	Age (in Years)	Sex	FNAC Site	Leukemia (Old/New Case)	Organomegaly (Yes/No)	Symptoms and Other Findings
1	28	Male	Inguinal lymph node	New	No	Abdominal pain and bilateral groin swellings
2	38	Female	Thigh swelling	Old	No	Vomiting, generalized weakness
3	70	Male	Inguinal lymph node	New	No	Decreased appetite, weight loss
4	60	Male	Inguinal lymph node	Old	Yes	Cough, shortness of breath, and feet swelling
5	6	Female	Pleural fluid	New	Yes	Abdominal pain and distension, decreased appetite, and shortness of breath
6	53	Female	Supraclavicular lymph node	New	Yes	Fever, reduced appetite, and weight loss
7	33	Male	Cervical lymph nodes	New	Yes	Fever, weight loss, and abdominal pain
8	45	Female	Purpuric lesions	Old	No	Fever, weight loss
9	46	Female	Cervical lymph node	New	No	Fever, weight loss

3. Dicussion

Generalized or localized lymphadenopathy can occur before or alongside leukemia but is relatively uncommon. In leukemia, the lymph nodes can be infiltrated by leukemia cells at any stage of the disease, during its progression, before the onset of marrow leukemia, or during relapse. Extramedullary hematopoiesis (EMH) happens when bone marrow function is inadequate or compromised. This condition is often secondary to various hematological disorders such as myelofibrosis, thalassemia and infiltrative disorders such as lymphomas. Lymph node involvement in leukemia and EMH is a well-known phenomenon.[6] Leukemic infiltration occurs in the liver, spleen, muscles, eye, pleural space, and skin.[1-4] The diagnosis of leukemic lymphadenopathy is crucial for treatment planning. FNAC diagnosis is straightforward in patients already diagnosed with leukemia. In suspected cases of lymphoproliferative disorders, performing a peripheral smear and FNAC of the lymph nodes is recommended to detect leukemic infiltration, as demonstrated in the abovementioned case. This step is important because FNAC is often the initial investigation, and information on hematological status is typically unavailable. Cytomorphological evaluation of lymph nodes and other palpable lesions is often conducted for diagnostic clarification, usually between leukemia and lymphoma. Distinguishing between leukemic infiltration and lymphomatous involvement in lymph nodes using FNAC smears alone is challenging. However, diagnostic accuracy improves significantly when a patient's medical history and marrow diagnosis are known. Specific cytochemical studies have aided in the diagnosis of leukemic lymphadenopathy. Histological sections of the lymph nodes are not useful for diagnosing leukemic infiltration because of the lack of distinct morphological features.[7] Without relevant hematological investigations, FNAC smears may be misdiagnosed as non-Hodgkin lymphoma (NHL) or metastatic carcinoma. This scenario was observed in case 6 of the present series. In a previous study.[7] FNAC smears from the lymph nodes of 14 patients with acute lymphoblastic leukemia (ALL) were initially misdiagnosed as NHL. In four cases of ALL-L1, the smears showed a monomorphic population of large lymphocytes (two-three times the size of RBCs) with minimal cytoplasm, where the nucleus occupied the entire cell and exhibited smooth chromatin. These cases were initially diagnosed as NHL, large-cell, and non-cleaved types. Histopathological examination also suggested NHL. However, after considering the clinical history and marrow diagnosis, all cases were correctly reclassified as having leukemic infiltration. The accurate identification of cells was facilitated by Wright-Giemsa staining, which preserved cell morphology better in FNA smears than in biopsy material. Therefore, clinical and hematological findings are crucial to distinguish between leukemic smears and lymphomas. The diagnostic accuracy of FNAC for detecting extramedullary leukemic infiltration was studied by Chen et al.[8] Among the 65 patients examined, 24 had ALL, 25 had acute myelogenous leukemia (AML), 6 had chronic lymphocytic leukemia (CLL), and 10 had CML. The lymph node was the most common infiltration site, accounting for 73.8% of the cases. Detailed morphological assessment using an oil-immersion lens and examination of peripheral blood smears effectively distinguished leukemic infiltration from NHL. Enlarged lymph nodes are rare in CML patients.[9] Generalized lymphadenopathy can occur when leukemia transforms into an acute form (blastic transformation), caused by the infiltration or growth of immature myelocytic cells (myeloblasts) in the lymph nodes. In some cases, lymph node involvement was observed before blastic transformation in the bone marrow and blood. In CML cases, it is rare for a blast crisis to initially present at an extramedullary site, such as the lymph node, making differentiation from malignant lymphoma challenging on routine lymph node biopsy.[10] In these situations, FNAC of the lymph node can facilitate rapid diagnosis because of the clear morphological details of blasts and other granulocytic cells observed with the May-Grünwald-Giemsa (MGG) stain. Extramedullary involvement occurs in conditions such as CML, MDS, and AML, with AML most commonly exhibiting this through chloromas, named for their green color due to the enzyme myeloperoxidase. In CML, which progresses from a chronic phase to an accelerated phase and eventually to a blast crisis, extramedullary infiltration in the form of granulocytic sarcomas is rare and usually appears later in the disease. Granulocytic sarcomas that develop during the chronic phase of CML have a poorer prognosis and a higher likelihood of rapid transformation to the blastic marrow.[11] Although extramedullary infiltration with myeloid cells in CML is rare and typically associated with acute or chronic phases, our case demonstrated such involvement during the stable chronic phase without progression to the accelerated phase.

Leukemia cutis is a condition where leukemic cells invade the dermis, occurring in myeloid and lymphoid leukemia. Granulocytic sarcoma rarely presents as a skin nodule (leukemia cutis) in chronic myeloid leukemia (CML). The presence of leukemia cutis suggests a blast crisis and a worse prognosis, even if hematological indicators suggest a chronic phase.[12] Typically, asymptomatic leukemia cutis can manifest as localized or generalized lesions, including papules, plaques, and nodules, varying in color from purplish to brownish.[13] In their study, a patient who experienced a CML relapse presented with these symptoms. Similar findings were observed in case 8 in our series, in which leukemia cutis indicated a relapse of CML that was successfully managed with imatinib. Hematological malignancies, such as acute and chronic leukemia, rarely result in or progress to pleural effusion during their clinical course. Detection of leukemic cells in pleural effusions as an initial morphological sign of the disease is particularly uncommon. Hodgkin's and non-Hodgkin's lymphomas are the predominant hematolymphoid malignancies associated with pleural involvement, occurring in 20–30% of cases, especially in cases of mediastinal involvement.[14] They presented a case study of a 26-year-old woman who presented with unilateral pleural effusion and was diagnosed with hematologic malignancy based on pleural fluid cytology. Subsequent investigations confirmed the diagnosis of acute myeloid leukemia. In our case series, we encountered a similar case involving a 6-year-old girl who was subsequently diagnosed with ALL. This case underscores the critical role of cytopathology in diagnosing rare and atypical presentations of hematologic malignancies. To summarize, this study discusses the challenges of diagnosing leukemic infiltration in lymph nodes, particularly in chronic myeloid leukemia (CML), where extramedullary involvement is rare and often mimics malignant lymphoma. It emphasizes the importance of fine-needle aspiration cytology (FNAC) combined with clinical history and hematological tests for accurate diagnosis. The study highlights the need for careful differentiation between leukemia and lymphoma, as FNAC alone may lead to misdiagnosis, especially in blast crisis or extramedullary infiltration cases.

4. Conclusion

Leukemic extramedullary infiltration can occur at various disease stages and sites, requiring regular monitoring. FNAC is a valuable diagnostic tool, but its accuracy improves with peripheral smear examination and patient history. Misdiagnosis can occur if relying solely on FNAC, necessitating a comprehensive diagnostic approach. Extramedullary involvement, such as leukemia cutis or pleural effusion, can indicate early progression or relapse, emphasizing the importance of monitoring various organ systems. In CML, extramedullary infiltration often signifies poor prognosis and rapid

progression, requiring aggressive treatment. FNAC is crucial in diagnosing rare and atypical presentations of hematological malignancies. Interdisciplinary collaboration is vital for accurate diagnosis and effective management of complex leukemia cases with extramedullary involvement.

Conflict of Interest

The authors declared that there is no conflict of interest.

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