# Blastic plasmacytoid dendritic cell neoplasm in children: diagnostic features and clinical implications

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## Supplementary Appendix

### *Cases reviewed at the National Cancer Institute: clinical summaries*

*Case one*

A 9-year old male presented with a subcutaneous mass involving the left calf as well as inguinal lymphadenopathy. Excisional biopsy of the calf mass demonstrated a well-circumscribed infiltrate sparing the epidermis. The lymph node biopsy demonstrated effacement by atypical cells morphologically similar to those in the calf biopsy. Cytogenetic analysis detected the presence of t(1;6). A staging bone marrow biopsy was negative for malignancy. The patient received vincristine, doxorubicin, cyclophosphamide, and prednisone as per Pediatric Oncology Group protocol 9219 for localized non-Hodgkin's lymphoma, achieving a complete remission. However, the disease recurred 9 months later as a subcutaneous mass in the left posterior thigh. The tumor was resected, and the patient received acute lymphoblastic leukemia (ALL)-type therapy (vincristine, prednisone, dexamethasone, daunorubicin, doxorubicin, cytosine arabinoside, L-asparaginase, 6-mercaptopurine, 6-thioguanine, cyclophosphamide, and methotrexate), according to the Children's Cancer Group protocol 1882.[1] Testicular involvement was discovered 18 months after the first recurrence, and the patient was treated with two courses of ifosfamide, carboplatin, and etoposide (ICE) and local radiation. The patient then underwent unrelated umbilical cord blood transplantation and developed grade 2 acute graft-*versus*-host disease of the skin, which resolved. This case was previously described, and the patient reportedly remains free of disease 13 years after diagnosis.[2]

*Case two*

A 4-year old female presented with a solitary right leg mass with mauve discoloration, measuring 6 x 4 cm. The biopsy revealed a nodular and diffuse atypical infiltrate in the dermis and subcutis, sparing the overlying epidermis. In addition to being positive for CD4, CD56, and CD123, the neoplastic cells were positive for plasmacytoid dendritic cell markers CD303/BDCA-2, TCL1, and CD2AP (Figure 1). The Ki-67 proliferative fraction was moderately high (2+/4). Surprisingly, S-100 appeared positive in a significant fraction of the neoplastic cells (Figure 1B), but tumor cells were negative for CD1a, langerin, synaptophysin, and chromogranin. No disease was identified elsewhere. The patient underwent surgical excision and multi-agent chemotherapy with three cycles of vincristine, doxorubicin, cyclophosphamide, and

**Online Supplementary Table S1. AML cases tested and negative for S-100 protein.**

| Bone marrow biopsies (Sex, age, diagnosis) |
|---|
| Male, 62, acute myeloid leukemia-not otherwise specified |
| Female, 63, acute myeloid leukemia-not otherwise specified |
| Male, 46, acute myeloid leukemia-not otherwise specified |
| Female, 84, acute myeloid leukemia-M1 |
| Male, 76, acute myeloid leukemia-M1-M2 |
| Male, 71, acute myeloid leukemia-M1-M2 |
| Female, 65, acute myeloid leukemia-M1-M2 |
| Male, 40, acute myeloid leukemia-M2 |
| Female, 50, acute myeloid leukemia-M2 |
| Female, 40, acute myeloid leukemia-M3 |
| Male, 44, acute myeloid leukemia-M3 |
| Male, 40, acute myeloid leukemia-M4 |
| Female, 73, acute myeloid leukemia-M5 |
| Male, 43, acute myeloid leukemia-M5 |
| Male, 63, acute myeloid leukemia-M5 |
| Male, 32, acute myeloid leukemia-M5 |
| Female, 64, acute myeloid leukemia-M6 |
| Male, 70, acute myeloid leukemia-M6 |
| **Skin biopsies** |
| Male, 78, acute myeloid leukemia-not otherwise specified |
| Male, 15, acute myeloid leukemia-M3 |
| Male, 49, acute myeloid leukemia-M5 |
| Female, 45, acute myeloid leukemia-M5 |
| Female, 42, acute myeloid leukemia-M5 |
| Male, 49, acute myeloid leukemia-M5 |
| Male, 50, acute myeloid leukemia-M5 |
| **Other sites** |
| Central nervous system- F, 10, AML-not otherwise specified |
| Lymph node- M, 65, AML-M5 |
| Mesenteric lymph node- M, 67, AML-M5 |

prednisone and one dose of PEG-asparaginase. The patient has remained free of disease for 11 years.

*Case three*

A 10-year old male presented with a 3-month history of facial swelling and pain, and radiographic studies demonstrated a destructive lesion of the maxilla. A biopsy of the maxillary mass demonstrated a diffuse atypical infiltrate that was positive for CD4, CD56, CD123, CD303/BDCA-2, TCL1, CD2AP, and S-100. No disease was identified elsewhere, and the patient received chemotherapy according to the Berlin-Frankfurt-Münster (BFM)-98 ALL regimen, which is similar to BFM-95 and includes intrathecal triple therapy (methotrexate, cytosine arabinoside, and hydrocortisone) without cranial radiation.[3] The patient achieved a complete remission and, at his last documented visit, had remained in remission for 5 years.

*Case four*

A 15-year old female presented with a painful erythematous, indurated patch on the left lower leg and palpable left inguinal lymphadenopathy. Biopsy of the skin lesion demonstrated an extensive atypical hematopoietic infiltrate in the dermis and subcutis, sparing the epidermis, positive for CD4, CD56, S-100, CD123, CD303/BDCA-2, TCL1, and CD2AP (Figure 2). Langerin and CD68 were negative. The Ki-67 proliferative rate was moderately high (2-3+/4). Flow cytometric studies on an involved inguinal lymph node additionally demonstrated positivity for HLA-DR (bright) and CD33 (dim), and negativity for CD16, CD57, CD19, CD22, CD11b, CD11c, CD13, CD14, and CD64. Magnetic resonance imaging, positron emission tomography scans, bone marrow biopsy and cerebrospinal fluid cytology did not reveal any other sites of disease. The erythrocyte sedimentation rate and lactate dehydrogenase levels were both modestly increased. The patient was treated with an aggressive chemotherapy regimen minimally modified from the BFM-90 protocol for patients with T-lymphoblastic lymphoma, with administration of intramuscular rather than intravenous L-asparaginase.[4] She had an excellent response to induction therapy, documented by positron emission tomography scans at day 33. Based on this result and the fact that at diagnosis she had not had evidence of bone marrow or central nervous system involvement, the patient was not given any radiation therapy and was treated according to Stage III stratification. Seven years after the original diagnosis she remains alive and well without evidence of disease.

*Case five*

A 7-year old female presented with an 8-month history of a right-sided forehead skin nodule, which appeared red-purple and measured 2.2 x 2 cm at the time of biopsy. Biopsy sections demonstrated a patchy dermal and extensive subcutaneous atypical mononuclear infiltrate. Imaging studies, bone marrow biopsy, and lumbar puncture did not reveal any evidence of other sites of disease. The patient was treated with induction chemotherapy according to Pediatric Oncology Group protocol 9315 with vincristine, doxorubicin, prednisone, and intrathecal methotrexate. This was followed by consolidation with ifosfamide/etoposide and cytosine arabinoside/idarubicin according to Pediatric Oncology Group protocol 9411. She achieved a complete remission and underwent stem cell transplantation 4 months after the diagnosis had been made. One year after the original diagnosis, the disease recurred with multiple bony lesions, involving the left femoral condyle and metaphysis, proximal tibial metaphysis, and right mid tibia, as well as ulcerated skin lesions on the extremities. Bone marrow aspirate and lumbar puncture were negative. Interestingly, examination of the ulcerated skin biopsies demonstrated that, in contrast to the original immunophenotype, some of the blasts were positive for myeloperoxidase, with variable lysozyme expression, and negative for CD56, consistent with "phenotypic conversion" to acute myeloid leukemia, although development of a second unrelated neoplasm is also possible. Given the extent of disease and multiple infectious complications, the patient was treated with palliative care that included chemotherapy. The patient developed respiratory syncytial virus-associated pneumonia and died 23 months after the initial diagnosis.

*Case six*

A 12-year old female presented with a 12 cm ulcerated cutaneous lesion on the right leg. The mass had grown slowly over the several months preceding the biopsy. Sections demonstrated an extensive infiltrate effacing the dermis and extending into the epidermis and subcutis. Bone marrow biopsy revealed blastic plasmacytoid dendritic cell neoplasm, although peripheral blood involvement was not apparent at the time of diagnosis. The patient underwent a Berlin-Frankfurt-Munster-based protocol for high-risk ALL with dramatic improvement of the skin lesion but persistence of bone marrow involvement. The patient died 6 months after diagnosis from infectious complications.

*Case seven*

A 7-year old male presented with a right thigh mass, measuring approximately 4 cm and, as demonstrated by magnetic resonance imaging, primarily confined to the subcutaneous soft tissue. Biopsy sections of the lesion demonstrated nodules and sheets of intermediate-sized atypical cells with a moderately high Ki-67 proliferative rate (2-3+/4). Bilateral inguinal lymphadenopathy was also present, but no other lesions were identified. Bone marrow biopsy and cerebrospinal fluid cytology were negative at the time of diagnosis. The patient received intensive ALL-like therapy, which consisted of induction with vincristine, daunorubicin, prednisone, and asparaginase, consolidation with cyclophosphamide, 6-mercaptopurine, and cytosine arabinoside, intrathecal methotrexate, hydrocortisone, and cytosine arabinoside, and maintenance. He remains in complete remission 14 months after diagnosis, and a follow-up biopsy was negative for residual malignancy.

*Case eight*

An 8-year old male with a history of eczema presented with a subcutaneous mass involving the left calf and inguinal lymphadenopathy. His complete blood count and chemistry panel, including serum lactate dehydrogenase, were within normal limits. No splenomegaly was noted on examination or imaging. Biopsy sections of the left calf tumor demonstrated an atypical mononuclear infiltrate sparing the epidermis, with a patchy, perivascular distribution in the dermis and forming expansile

sheets in the subcutis. A bone marrow biopsy demonstrated involvement by disease, whereas the cerebrospinal fluid was negative. High-risk ALL-type therapy was initiated, which promptly led to remission (day 29). Nine months after diagnosis, the patient appears to remain free of disease on maintenance chemotherapy.

*Case nine*

A 9-year old male who had been treated for 9 months with methotrexate and 1 month with etanercept for juvenile rheumatoid arthritis presented with cervical lymphadenopathy and was found to have pancytopenia. Further examination revealed a skin lesion on the right forearm, and biopsy of this lesion led to the diagnosis of blastic plasmacytoid dendritic cell neoplasm. A bone marrow biopsy showed involvement by the neoplasm. Since the diagnosis was very recent, additional clinical follow-up data are not available.

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