A unique case of mixed phenotype acute leukemia with t(9;22)(q34.1;q11.2);BCR-ABL1 sarcoma with epitheliotropism mimicking intestinal T cell lymphoma

Carol Wang¹ · Luke Shier² · Diponkar Banerjee³ · Philip Berardi³ · Bruce F. Burns³ · Aleksandra Paliga³

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Abstract

Myeloid sarcomas and extramedullary manifestations of mixed phenotype acute leukemia (MPAL) without leukemic involvement are rare. We present an unusual case of myeloid sarcoma of T/myelomonocytic biphenotypic nature and *BCR-ABL1* translocation demonstrating an epitheliotropism in the gastrointestinal tract and mass-forming lesions in the lungs without bone marrow involvement. A 69-year-old gentleman presented with non-bloody diarrhea and abdominal pain complicated by weight loss. CT scan showed diffuse mural thickening in the jejunum, distal ileum, transverse colon, and splenic flexure and bilateral pulmonary nodules. Biopsies of the ileum and colon were performed. An initial diagnosis of T cell lymphoma was made based on intestinal infiltration with CD4 and CD7 positive monomorphic atypical cells. Despite treatment, the patient's lung masses grew. A comprehensive immunohistochemistry panel was performed on the lung biopsy based on the classic morphologic appearance of sheets of atypical cells and that CD4 and CD7 are also expressed in a subset of myeloid cells. The panel demonstrated CD34 (subset), CD68, muramidase/lysozyme, and CD117 expressions. Flow cytometry showed an aberrant myelomonocytic population. The presence of T lineage blasts was confirmed by a subset of blasts with cytoplasmic CD3. The diagnosis of mixed phenotype T/myeloid sarcoma with myelomonocytic differentiation and t(9;22)(q34.1;q11.2);*BCR-ABL1* was made. Epitheliotropism has not been previously described as a histologic feature of intestinal myeloid sarcomas. The epitheliotropism, enteropathy-like features and gastrointestinal symptoms mimicked T cell lymphomas. This case highlighted the pivotal role of flow cytometry and clinicopathological correlation in making a diagnosis of myeloid sarcoma with MPAL phenotype.

Keywords Hematopathology · Myeloid sarcoma · Epitheliotropism

Introduction

Myeloid sarcoma is an extramedullary mass of immature myeloid blasts, which typically coexist with myeloid cells in

various stages of maturation that infiltrate and efface tissue [1, 2]. The diagnosis of myeloid sarcomas has been classified into (a) myeloid sarcomas in isolation, (b) coexistence of myeloid sarcoma with acute myeloid leukemia (AML), (c) AML relapsing as extramedullary manifestation, and (d) presentation of myeloproliferative neoplasm and/or myelodysplastic syndrome undergoing blast transformation [3]. The World Health Organization also describes mixed phenotype acute leukemias (MPAL) as a rare heterogeneous group of acute leukemias including bilineal and biphenotypic leukemias [4]. The presence of one blast population with coexpression of markers specific for more than one lineage is a defining feature of biphenotypic leukemias. In contrast, bilineal leukemias are characterized by the presence of two discrete blast populations, each meeting the criteria for a different lineage [4, 5]. Blast immunophenotyping and thus the diagnosis of MPAL are based primarily on multi-parameter flow cytometry [5, 6]. Although rare, both myeloid

✉ Carol Wang
carwang@toh.ca

¹ Division of Anatomical Pathology, Department of Pathology and Laboratory Medicine, University of Ottawa, CPC 162 737 Parkdale Avenue, Ottawa, ON K1Y 1J8, Canada
² Division of Hematopathology, Eastern Ontario Regional Laboratory Association and Department of Pathology and Laboratory Medicine, University of Ottawa, Ottawa, ON, Canada
³ Division of Anatomical Pathology, Eastern Ontario Regional Laboratory Association and Department of Pathology and Laboratory Medicine, University of Ottawa, Ottawa, ON, Canada

sarcomas and extramedullary manifestations of MPALs without leukemic involvement have been described in literature. We present an unusual case of myeloid sarcoma of T/myelomonocytic biphenotypic nature and *BCR-ABL1* translocation demonstrating an epitheliotropism in the gastrointestinal tract and mass-forming lesions in the lungs without bone marrow involvement.

Clinical history

A 69-year-old gentleman with a remote history of pT3aN0 prostate cancer treated with radical prostatectomy and adjuvant radiation and hormone therapy presented with a 3–4 months history of non-bloody diarrhea, abdominal pain, poor appetite, and malaise complicated by a 50-lb weight loss. Infectious etiologies were ruled out with stool cultures that were negative for salmonella, shigella, Yersinia, campylobacter, E coli, ova, and parasites. He subsequently underwent upper endoscopy and colonoscopy, which showed scattered small punctate areas of inflammation throughout the colon, although sparing the distal rectum. The endoscopic impression of colitis was raised, pending final diagnosis based on biopsy results. Biopsies taken from the duodenum, terminal ileum, and colon showed infiltration by a rather monomorphic population of atypical cells with irregular nuclear membranes and inconspicuous nucleoli that were identified in variable numbers within the lamina propria of all three biopsy sites. Interestingly, the atypical infiltrate demonstrated epitheliotropism (Fig. 1). On immunohistochemistry, these atypical cells were positive for CD4 and CD7, but negative for CD3, CD5, CD8, CD20, CD30, and CD56. Based on the presence T cell markers in association with epitheliotropism, the surgical pathologist made a diagnosis of intestinal T cell lymphoma not otherwise specified (NOS).

Further investigations showed a CBC with a slight reactive neutrophilia and negative anti-tissue transglutaminase IgA antibody. Staging workup with CT scan showed the presence of diffuse mural thickening in the jejunum, distal ileum, distal transverse colon, and splenic flexure as well as multiple

mesenteric lymph nodes. CT chest revealed multiple bilateral pulmonary nodules ranging in density from ground glass opacities to solid nodules as well as a hilar lymphadenopathy, which were FDG avid on PET scan. Most notably, there was interval progression in the size of these nodules especially in the left lower lobe measuring 3.9 cm × 2.9 cm despite cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone (CHOP) chemotherapy. In review of the PET scan findings, there was concern for a separate malignant process in the lungs. In the interim, CHOP chemotherapy regimen was continued pending biopsy of the lung mass. His gastrointestinal symptoms remained refractory to chemotherapy.

Results

Biopsy of the left lower lobe mass and repeat endoscopic biopsies of the ileum and colon performed 3 months after the diagnosis of intestinal T cell lymphoma showed diffuse infiltration of the lung parenchyma with atypical medium-sized cells that were cytomorphologically identical to those present in the intestinal biopsies. The more classic presentation as a mass-like lesion in the lung and lack of response to treatment led to re-evaluation of the diagnosis. Additional immunohistochemical stains were performed in consideration of a myeloid sarcoma. In addition to CD4 and CD7 expression, the atypical cells were also positive for CD34 (subset), CD68, muramidase/lysozyme, and CD117 (Fig. 2). The diagnosis of myeloid sarcoma was raised and tissue for flow cytometry and cytogenetics/molecular testing was requested. Flow cytometry of the lung biopsy showed an aberrant monocytic population with variable immaturity. Blasts accounted for 70–90% of nucleated cells. Myelomonocytic differentiation was confirmed based on blast expression of CD11c and CD64, with concurrent CD11c, dim CD13, bright CD33, dim CD71, partial CD117, and partial CD34 positivity. The blast population was myeloperoxidase negative. A distinct subset of blasts with strong cytoplasmic CD3 was identified comprising 10% of the analyzed blast population, confirming the

Fig. 1 **a, b** Ileum biopsy demonstrates diffuse infiltration of medium sized atypical lymphocytes throughout the lamina propria with villous blunting and epitheliotropism of the intestinal villi and crypts. (hematoxylin-eosin, original magnifications × 20 (**a**) and × 400 (**b**))

Fig. 2 Intestinal biopsy immunohistochemical stains: **a** Epitheliotropism with atypical lymphocyte infiltration into crypts and lamina propria. The cells are negative for CD3, which highlights the scattered normal T cells (**a**); CD7 positive (**b**); CD117 dim positive (**c**), and lysozyme partial positive (**d**). (Original magnifications $\times 200$ (**a–d**))

presence of T lineage blasts (Fig. 3). Bone marrow aspirate and trephine biopsy showed no evidence of marrow involvement. Furthermore, genetic testing for *BCR-ABL1*, t(9;22) translocation was positive. Hence, the diagnosis of sarcoma with mixed phenotype acute leukemia (T/myeloid) differentiation with t(9;22)(q34.1;q11.2);*BCR-ABL1* was made. Unfortunately, the patient deteriorated rapidly and declined further treatment.

Discussion

This case describes a patient with myeloid sarcoma without concurrent AML manifesting as an epitheliotropic diffuse gastrointestinal infiltrate and mass-forming lesions in the lungs. It is a unique form of myeloid sarcoma with biphenotypic blast population detected on flow cytometry as well as *BCR-ABL1* translocation. The WHO has placed great emphasis on the presence of cytoplasmic or surface CD3 for the isolation of a T cell lineage. Expression of CD3 must be strong, comparable to that seen on mature T cells, but no threshold for the proportion of blasts expressing CD3 is provided [4]. In our case, the detection of CD3 expression by the blast population was not appreciated on immunohistochemistry but rather became apparent on flow cytometry, emphasizing the role of a comprehensive cytometry workup.

Extramedullary manifestations of MPALs and myeloid sarcomas without leukemic involvement are rare. While myeloid sarcomas have a predilection for subcutaneous tissue, bone, lymph nodes, gastrointestinal tract, and central nervous system, extramedullary MPALs occur more frequently in the central nervous system [7–11]. Gastrointestinal presentation of primary

myeloid sarcoma without bone marrow involvement is rare and often reported in case reports and case series [2, 7, 12–14]. Myeloid sarcoma of the gastrointestinal tract most commonly occurs in the ileum [12]. Diagnostic imaging and intraoperative findings in the majority of reported cases in the literature are mass/tumor forming lesions complicated by intestinal obstruction while diffuse bowel wall thickening is seldom reported [2, 7, 12–14]. Histologically, tumor cells diffusely infiltrate the intestinal wall and are associated with destruction of the underlying architecture [13]. Extranodal myeloid sarcoma is known to mimic metastatic carcinomas with cohesive nests or the formation of single files enclosed by fibrous septa [1]. Epitheliotropism is not a documented characteristic of myeloid sarcoma in the intestine. In contrast to myeloid sarcoma, extramedullary non-leukemic biphenotypic myeloid sarcomas with manifestation in the gastrointestinal tract have not yet been described [15–19].

De novo myeloid sarcomas without leukemic involvement are difficult to diagnose and case series have reported up to 47% misdiagnosed as lymphomas, myelomas, Ewing sarcoma, and carcinomas [3, 7]. It has been suggested that inadequate immunophenotyping is a contributor to its diagnostic difficulties [20]. In our case, demonstration of CD68 and CD117 immunohistochemical staining on the latter biopsy taken from the lung mass raised the possibility of a myeloid sarcoma. Another element of diagnostic difficulty that was unique to our case was the epitheliotropism displayed by the blasts. Diffuse infiltration of atypical mononuclear cells in the lamina propria as well as enteropathy-like features with villous blunting and intraepithelial lymphocytes are characteristic features of gastrointestinal tract T cell lymphomas such as enteropathy associated T cell lymphoma (EATL), monomorphic epitheliotropic intestinal T cell lymphoma (MEITL), and

Fig. 3 Flow cytometric immunophenotyping of the lung tissue revealed a blast population with relatively bright CD45 and variable side scatter (a). Blasts show partial CD34 and partial CD117 expression (b), along with bright expression of CD33 and coexpression of CD7 (c). Monocytic differentiation is shown with expression of CD64 (d) and CD11c, although CD14 negative (e). A distinct subset of blasts shows

coexpression of CD33 with strong cytoplasmic CD3 (f). B lineage markers CD10, CD19, cytoplasmic CD22, and cytoplasmic CD79a were negative (data not shown). Blasts are colored red, CD34 positive subset gold, monocytic subset magenta, granulocytes cyan, and mature lymphocytes green

indolent T cell lymphoproliferative disorders of the gastrointestinal tract [21–24]. Clinically, these T cell lymphomas share similar presentations with gastrointestinal symptoms such as diarrhea, abdominal discomfort, food intolerances, and weight loss [21–24]. Epitheliotropism has not been described in literature as a histologic feature of intestinal presentations of myeloid sarcomas. Perhaps the minor T cell component of this myeloid sarcoma conferred it with its epitheliotropic features. Our experience has highlighted the pivotal role of flow cytometry as well as clinicopathological correlation in making a diagnosis of myeloid sarcoma with MPAL phenotype.

Prior history of radiation therapy to the pelvis is associated with secondary malignancies especially bladder, colorectal, dermatological cancers, and lymphomas [25, 26]. Secondary leukemias, especially acute myeloid leukemia, are increased by two to threefold, with peak incidence 5–10 years following pelvic radiation [27]. However, the risk of MPAL in a patient with prior history of radiation therapy is unknown. MPAL is a rare entity that makes up 2–5% of acute leukemias, incidence varying based on the diagnostic algorithm used [5, 28, 29]. The disease entities are known to occur in both adults and

pediatric populations, with a slight male predominance [4, 5, 29]. The high-risk genetics associated with multilineage expression confers a poor prognosis [5]. Two genetically distinguished MPAL entities are recognized in the WHO, MPAL with t(9;22)(q34.1;q11.2); *BCR-ABL1* and MPAL with t(v;11q23.3); *KMT2A* or *MLL*-rearranged [4]. Genetic testing on our patient confirmed the *BCR-ABL1* mutation, conferring a diagnosis of myeloid sarcoma of MPAL type with t(9;22); *BCR-ABL1*, which is the more common genotype in adults [30, 31]. Patients with this genotype account for < 1% of acute leukemias with a male predominance and usually present with leukocytosis [4, 30]. Thought to be derived from a multipotent hematopoietic stem cell that differentiates into lymphoid and myeloid lineages, most cases present with a dimorphic blast population that resemble lymphoblasts and myeloblasts [4, 11]. While a B/myeloid phenotype predominates, there are rare cases of T/myeloid in this MPAL subtype [4]. *BCR-ABL1* translocation portends a worse prognosis compared to other MPAL subtypes [4, 31–34]. In a study of 21 Chinese patients with t(9;22) or *BCR-ABL1* MPAL patients with B/myeloid phenotype, the 1-year overall survival was 28%

[31]. Its aggressive behavior is attributable to its ability for lineage plasticity, although less common in *BCR-ABL1* compared with the *KMT2A* subtypes [5].

Gastrointestinal myeloid sarcoma without leukemic involvement is a rare entity that often presents as a mass. Without a high index of suspicion, this diagnosis may be overlooked, especially in cases where an identifiable mass is absent. Flow cytometry and a comprehensive immunohistochemistry panel including antigens most frequently expressed in myeloid sarcoma (CD43, CD68, lysozyme, myeloperoxidase, and CD117) are essential in making the correct diagnosis. We present a unique case of myeloid sarcoma with MPAL of T/myelomonocytic biphenotypic nature and t(9;22)(q34.1;q11.2);*BCR-ABL1* translocation demonstrating an unusual epitheliotropism in the gastrointestinal tract as the first reported case.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflicts of interest.

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