Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN): a Closer Look

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A case...

• An otherwise healthy 58 year-old man was found to have thrombocytopenia of 99,000 in 2012 but was asymptomatic, and an immune cause was suspected.
• In summer 2015, he developed progressive fatigue.
• At visit with hematology in October 2015, CBC showed WBC of 11,000, Hgb 12.4, Plt of 53,000.
• In November, counts declined to WBC 8100, Hgb 11.3, Plt of 41,000. Differential showed 36% monocytes.
• A bone marrow biopsy was performed.
A biopsy...

Bone marrow biopsy, aspirate smears, touch preparation, clot section, and peripheral blood smear:
1. Hypercellular marrow involved by a myeloid stem cell neoplasm, favor chronic myelomonocytic leukemia (CMML-1) with increased abnormal plasmacytoid dendritic cells; see comment.
2. Peripheral blood with anemia, thrombocytopenia, and absolute monocytosis.

COMMENT:
Thank you for the opportunity to review this challenging case in consultation. The findings of a hypercellular marrow with clusters of plasmacytoid dendritic cells and 3.5% myeloid blast in the setting of anemia, thrombocytopenia, and a persistent monocytosis are consistent with involvement by a myeloid stem cell neoplasm and favor classification as chronic myelomonocytic leukemia (CMML-1). Clusters of plasmacytoid dendritic cells (PDCs) may be seen in the setting of CMML, and on the basis of morphology (with aggregates of PDCs comprising approximately 5-10% of the marrow cells), the clusters of PDCs seen in this case are favored to be related to an underlying CMML. However, PDC aggregates seen in the setting of CMML are typically CD56 negative, while the PDCs present in this patient are CD56 positive. CD56 may occasional be seen on reactive monocytic cells and PDCs; however, the expression of CD56 on PDC also raises consideration for a blastic PDC neoplasm. At this time point, the marrow findings are NOT considered sufficient for diagnosis of a blastic PDC neoplasm.
The case continues...

• With a working diagnosis of CMML-1, the patient moved forward with azacitidine treatment.
• At initial SCCA consultation in early 2016, he was recommended to consider stem cell transplant as only curative treatment. The patient also noted some visual disturbances at that time.
• When seen by ophthalmology, he was noted to have bilateral retinal detachments concerning for leukemic involvement.
• Lumbar puncture was performed with IT methotrexate, skin biopsy from August 2015 was obtained for internal review, and a repeat bone marrow biopsy was performed.
More biopsies and a diagnosis

Skin, right neck, biopsy:
Involvement by a myeloid neoplasm (see comment).

COMMENT:
The combined morphologic and immunocytochemical studies demonstrate a dermal infiltrate which predominantly consists of atypical appearing monocytes that express lysozyme, CD68, CD4, and CD56 and lack expression of CD34, CD117 and myeloperoxidase. Plasmacytoid dendritic cells, identified by CD123 positivity, are scattered and focally clustered without evidence of CD56 coexpression. Taken together, these findings demonstrate cutaneous involvement by a myeloid neoplasm with monocytic differentiation. Whether this process is best categorized as a de-novo myeloid sarcoma or cutaneous involvement by an underlying myeloid stem cell neoplasm (i.e. skin involvement by the subsequently diagnosed CMML) is more difficult to determine. If clinically indicated, an involved skin biopsy

RESULT SUMMARY:
Chromosome Genomic Array Testing (CGAT) results with a Male genotype:
Deletion of 4q24- (451 Kb) in >80% cells leading to partial deletion of TET2, most likely somatic

INTERPRETATION
Cerebrospinal fluid: Small population of plasmacytoid dendritic cells with CD56 expression, see comment

COMMENT
The flow cytometry study identified a population of plasmacytoid dendritic cells (pDCs), which represents approximately 2% of white cells and shows coexpression of CD4, CD7 (partial), CD56, CD123 and HLA-DR without significant CD5, CD13, CD14, CD15, CD16, CD19, CD33, CD34, CD64, CD71, or CD117. The myelomonocytic populations have normal mature immunophenotype. CD56 expression is usually absent on normal pDCs in bone marrow and characteristics for blastic plasmacytoid dendritic cell neoplasm (BPDCN).
A brief history of BPDCN

1994: First description of CD4+/CD56+ neoplasms, thought to be a cutaneous lymphoma. Found to have an aggressive clinical course.


1999: Initial description of plasmacytoid dendritic cells (pDCs).


2001: WHO classification suggests “blastic NK cell tumor” for CD56+ malignancies with precursor-like morphology.
A brief history of BPDCN - finding your long-lost parents.

A brief history of BPDCN

1990: First description of CD4+/CD56+ neoplasms, thought to be a cutaneous lymphoma. Found to have an aggressive clinical course.


1999: Initial description of plasmacytoid dendritic cells (pDCs)


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2001: WHO classification suggests “blastic NK cell tumor”.


2008: Blastic plasmacytoid dendritic cell neoplasm established as WHO diagnosis.

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WHO?

2008:

Acute myeloid leukemia and related neoplasms
  Acute myeloid leukemia with recurrent genetic abnormalities
  AML with t(8;21)(q22;q22); RUNX1-RUNX1T1
  AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11
  APL with t(15;17)(q22;q12); PML-RARA
  AML with t(9;11)(p22;q23); MLLT3-MLL
  AML with t(6;9)(p23;q34); DEK-NUP214

  Myeloid leukemia associated with Down syndrome
  Blastic plasmacytoid dendritic cell neoplasm

2016:

Acute myeloid leukemia (AML) and related neoplasms
  AML with recurrent genetic abnormalities
  AML with t(8;21)(q22;q22); RUNX1-RUNX1T1
  AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11
  APL with PML-RARA
  AML with t(9;11)(p21.3;q23.3); MLLT3-KMT2A
  AML with t(6;9)(p23;q41.1); DEK-NUP214
  AML with inv(3)(q21.2q26.2) or t(3;3)(q21.2;q26.2); GATA2, MECOM
  AML (megakaryoblastic) with t(1;22)(p13.3;q13.3); EBMT15-MKL1

  Provisional entity: AML with BCR-ABL1
  AML with mutated NPM1
  AML with biallelic mutations of CEBPA
  Provisional entity: AML with mutated RUNX1
  AML with myelodysplasia-related changes
  Therapy-related myeloid neoplasms
  AML, NOS
  AML with minimal differentiation
  AML without maturation
  AML with maturation

In Table 1 (page 2392), the entry “Blastic plasmacytoid dendritic cell neoplasm” was omitted.

6. Blastic plasmacytoid dendritic cell neoplasm
  This is a new category that includes most cases previously classified as blastic NK-cell lymphoma/leukemia or agranular CD4+ CD56+ hematodermic neoplasm; it is derived from a precursor of plasmacytoid dendritic cells.

Arber et al, Blood 2016. 127(20): 2391-2405
Typical and atypical presentations

• BPDCN is a rare disease – only about 1000 cases per year in the U.S.
• Can affect children but median age of diagnosis is in 60s; found in men over women at 3:1.
• 90% of patients present with skin lesions.
• 10% present in leukemic phase – extensive bone marrow involvement, though often associated with skin lesions as well.
• In one prospective series of 13 patients WITHOUT neurologic symptoms, 6/10 newly-diagnosed patients and 3/3 relapsed-refractory patients had evidence of occult CNS involvement.
• In another retrospective set of 23 patients, IT prophylaxis at diagnosis was associated with improved CNS-RFS and OS.
Typical and atypical presentations

Diagnostic dilemmas

- Skin lesions can be difficult to distinguish from involvement by other hematologic malignancies.
- There can also be immunophenotypic overlap (e.g. CD56- BPDCN or CD56+ leukemia).
## Diagnostic dilemmas

<table>
<thead>
<tr>
<th></th>
<th>BPDCN</th>
<th>AML/LC/MS</th>
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</thead>
<tbody>
<tr>
<td><strong>SHARED</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4</td>
<td>80-100 %</td>
<td>10-20 %</td>
</tr>
<tr>
<td>CD56</td>
<td>90-100 %</td>
<td>5-50 %</td>
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<tr>
<td>CD123</td>
<td>85-100 %</td>
<td>15-45 %</td>
</tr>
<tr>
<td>TCL1</td>
<td>80-100 %</td>
<td>5-20 %</td>
</tr>
<tr>
<td><strong>UNIQUE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD2AP</td>
<td></td>
<td>MPO</td>
</tr>
<tr>
<td>CD303/Basca-2</td>
<td></td>
<td>Lysozyme</td>
</tr>
<tr>
<td>CD14</td>
<td></td>
<td>CD34</td>
</tr>
<tr>
<td>CD11c</td>
<td></td>
<td>CD163</td>
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</tbody>
</table>


With friends like these...

• About 10-20% of BPDCN patients have coexisting myeloid neoplasms such as MDS, CMML and AML.

• In one published case of an 82 year-old who developed cutaneous BPDCN after prior diagnosis of CMML, sequencing identified same mutation in TET2 and SRSF2, suggesting shared clonal origin.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Mutation</th>
<th>Consequence</th>
<th>VAF CMML</th>
<th>VAF BPDCN</th>
</tr>
</thead>
<tbody>
<tr>
<td>TET2</td>
<td>NM_001127208.2:c.3730_3731delCT</td>
<td>Y1244fs</td>
<td>50</td>
<td>38</td>
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<tr>
<td>TET2</td>
<td>NM_001127208.2:c.2428C&gt;T</td>
<td>Q810*</td>
<td>49</td>
<td>34</td>
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<tr>
<td>SRSF2</td>
<td>NM_001195427.1:c.284C&gt;A</td>
<td>P95H</td>
<td>46</td>
<td>37</td>
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<tr>
<td>JAK2</td>
<td>NM_004972.3:c.1849G&gt;T</td>
<td>V617F</td>
<td>15</td>
<td>not mutated</td>
</tr>
</tbody>
</table>
The case continues...

• Patient was admitted to hospital for G-CLAM induction therapy.
• Underwent a LP with IT cytarabine on D1.
• At D28, neither LP nor bone marrow biopsy showed active disease, consistent with CR.
• He then received G-CLA consolidation, complicated by CONS bacteremia.
• Subsequently referred to transplant service.
The initial treatment conundrum

- No standard induction therapy for BPDCN.
- Because of the rarity of the disease, both lymphoid and myeloid regimens have been used and no randomized trial exists.
- Most aggressive regimens are effective at achieving a CR, sometimes close to 90%.
- Though some trends toward better survival with ALL-type regimens, limited by small series and confounders.
The initial treatment conundrum

Figure 3. Overall survival (OS) according to types of induction therapy. The median OS was 12.3 months (range 1-32.9) in patients who received an ALL/lymphoma-type regimen and 7.1 months (range, 0.2-19.5) in those treated with an AML-type regimen (P=0.02).


Pagano et al, Haematologica 2013; 98(2):239-246
The case continues...

- The patient was referred to the transplant service, though arrival was delayed for donor availability issues.
- While awaiting transplant, he was given another cycle of G-CLA as consolidation.
- Prior to transplant, he developed a skin lesion biopsy positive for BPDCN involvement. Bone marrow biopsy was negative.
- Plan to move forward to transplant with focal irradiation to skin sites.
Transplant for BPDCN – a winning strategy?

• In the earliest retrospective studies of CD4+/CD56+ malignancies, the more aggressive the treatment strategy, the better the outcome.

• In a retrospective study of 34 patients receiving allo-SCT, 3-year OS was 41%, and being in CR1 had a positive effect on survival.

• Auto-SCT may also have a role; in a Japanese retrospective study of 25 patients, auto-HSCT patients and allo-SCT patients had 4 year OS rates of 82% and 53%, respectively.

• Most recently, a European study of 43 patients showed higher relapse risk, lower NRM and equivalent mortality in RIC vs. MAC regimens, with ~50% 2 year OS.

Relapsed and refractory disease and frail patients

• The majority of patients will relapse within despite achieving CR at a median of 5.5 months.
• Small case series exist of pralatrexate, azacitidine, and less-aggressive lymphoma-type therapy.
• One series of 3 relapsed-refractory patients, two after allo SCT, responded very well to gemcitabine/docetaxel, with median PFS of 10.6 months.
The case concludes.

- The patient was transferred to the care of the transplant service while neutropenic from prior G-CLA.
- The patient received radiation to his biopsy-proven skin involvement.
- Unfortunately then developed disseminated *Fusarium* infection and was transferred ultimately to hospice care.
- He passed away approximately 6 months after his diagnosis of BPDCN, and 9 months from diagnosis of CMML-1.
Prognosis in BPDCN

• Only transplant has been shown to provide long-term disease-free survival.
• Median survival of only 12-14 months for all comers.
• A clear need for further study and new therapies.
Genetic basis of BPDCN

• There has been significant interest in the clonal origin of BPDCN.
• In one series, TET2 was mutated in 7/14 patients, supporting myeloid origin.
• More recent whole exome sequencing identifies a range of mutations, some associated with poor prognosis.

Menezes et al, Leukemia 2014; 28:823-829
Molecular basis for new therapies

- Compared to normal pDCs, BPDCN cells show increase in NF-kB signaling and BCL2 expression, which can be shut off in vitro by bortezomib leading to apoptosis.

Sapienza et al, Leukemia 2014; 28: 1606-1616
BCL2 inhibition in BPDCN

• Cells and xenograft models of BPDCN have been shown to be sensitive to BCL2 inhibition by venetoclax.
• Two relapsed/refractory patients had dramatic cutaneous responses to treatment.

Montero et al, Cancer Discovery 2017; 7: 156-164
BET inhibitors for BPDCN

• More recently, BPDCN has been shown to be dependent on the transcription factor TCF4. Inhibition of downstream cellular activators by bromodomain and extra-terminal domain inhibitors (BETi) lead to in vitro cell toxicity.

• BETi also decrease expression of lincRNA-3q, a novel non-coding RNA involved in leukemia maintenance.

• Clinical trials still at the phase I level.

Emadali et al, Blood 2015; 127: 3040 - 3053
Antigen-targeted therapy for BPDCN

- Consistent and high expression levels of specific cell surface protein make BPDCN a potentially good target for immunotherapeutic approaches.
- Lorvotuzumab memtansine, an antibody-drug conjugate, is currently in Phase II trials in CD56+ malignancies.
SL-401

• BPDCN nearly universally expresses CD123, the IL-3 receptor.
• SL-401 is a fusion protein consisting of diptheria toxin linked to IL-3 designed to target IL-3R-expressing malignancies.
• In a phase 1-2 clinical trial, 7/9 patients had major responses (5 CRs, 2 PRs), lasting a median of 5 months.
• Primary toxicities include capillary leak.

Frankel et al, Blood 2014; 124: 385-392
SL-401

• Update on phase II registration study presented at ASH 2016: 13/16 (81%) of new patients achieved CR, and 4/13 (31%) of relapsed-refractory patients.

Here's Why Stemline Therapeutics Stock Fell 36.9% This Morning

What happened
Shares of Stemline Therapeutics (NASDAQ:STML) tumbled nearly 37% this morning after investors learned that a patient died in a clinical trial involving its lead drug candidate, SL-401. The news was not reported by the company, but confirmed by the patient’s family and first reported by Adam Feuerstein of TheStreet.

So what
Not hearing the news directly from management is bad enough, but the death occurred the day before a Jan. 19 stock offering for $45 million. Worse still, this is the third death to occur in a clinical trial involving SL-401 from a side effect known as capillary leak syndrome, a form of low blood pressure. The company had responded to previous patient deaths by altering dosing regimens, so the recent death hints that the drug may not be safe enough for human use in its current form or dosing.

Conclusions

- BPDCN is a rare hematologic neoplasm typically characterized by CD4, CD56 and CD123 expression.
- Skin involvement, present in most patients, can rapidly progress to bone marrow and CNS infiltration.
- Though standard treatments can effectively achieve remissions, SCT is the only effective means of achieving long-term RFS.
- Recent genetic studies have identified recurrent mutation pathways with prognostic and therapeutic significance.
- Multiple novel, targeted treatment approaches are showing promise in pre-clinical models and early clinical trials, though safety concerns exist.
Acknowledgments

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References


References


