

# Excessive Therapeutic Response in a Case of Blastic Plasmacytoid Dendritic Cell Neoplasm

Marie P. Shieh, MD<sup>1</sup>  
 Niloufar Reisian, MD<sup>2</sup>  
 V. Walavalkar, MD<sup>2</sup>  
 Lewis M. Slater, MD<sup>1</sup>  
 Nils Lambrecht, MD, PhD<sup>2</sup>

<sup>1</sup>Hematology-Oncology Section, Medicine Health Care Group Long Beach Veterans Affairs and Division of Hematology-Oncology and Department of Medicine;

<sup>2</sup>Pathology and Laboratory Medicine Service, Long Beach Veterans Affairs and Department of Pathology University of California, Irvine, California

## Case Report

A 65-year-old African American man had been followed in the hematology-oncology clinic since 2003 for monoclonal gammopathy of unknown significance (MGUS) and anemia. Bone marrow biopsy at the time of initial presentation was unremarkable. In August 2008, he began to develop violaceous cutaneous lesions, generalized lymphadenopathy, and pancytopenia. Punch biopsy of the left arm revealed superficial and deep perivascular and interstitial infiltrates of small- to intermediate-sized cells. A bone marrow biopsy in October 2008 showed infiltration of mononuclear cells of similar morphology and immunohistochemical phenotype (positive for CD4 and CD56). Additionally, flow cytometry of a cervical lymph node biopsy from the same month demonstrated a large population of cells expressing CD4, CD56, and CD123. Based on these findings, the diagnosis of blastic plasmacytoid dendritic cell neoplasm, formerly known as CD4-positive/CD56-positive hematodermic neoplasm or blastic natural killer cell lymphoma, was made.

From November 2008 to June 2009, the patient received 8 cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy, with a good response. His cutaneous lesions and palpable lymph nodes rapidly decreased in size after the third cycle. Positron emission tomography (PET)/computed tomography (CT) scans indicated complete response after the eighth cycle. However, in August 2009, while evaluation for stem cell transplantation was being arranged, he again developed similar extensive cutaneous lesions over his

face, scalp, trunk, and extremities (Figure 1, top panel). Repeat bone marrow biopsy indicated relapse.

On November 2, 2009, the patient began treatment with bortezomib (Velcade, Millennium Pharmaceuticals; 1 mg/m<sup>2</sup> on days 1, 4, and 8), dexamethasone (40 mg on days 1–4), and thalidomide (Thalomid, Celgene; 50 mg on days 1–21), with dramatic resolution of his cutaneous lesions by day 8 (Figure 1, bottom panel). However, on day 4, the patient required transfusion of packed red blood cells (pRBCs) and platelets before administration of chemotherapy, and on day 7, he developed multiple fevers of up to 101–102°F. Compared to an initial chest X-ray on day 4 to confirm placement of the peripherally inserted central catheter (PICC), a repeat chest X-ray on day 8 revealed a new right upper lobe infiltrate, and the patient was started on broad-spectrum antibiotics while thalidomide was discontinued. The patient's fevers persisted; he developed multi-organ failure and required intubation and hemodialysis. Due to his poor prognosis, his family withdrew care. The patient died 23 days after initiating chemotherapy.

## Materials and Methods

Skin, cervical lymph node, and bone marrow core biopsies, as well as the autopsy specimens, were fixed in 10% formalin and embedded in paraffin. Additionally, the marrow cores were decalcified for 30 minutes prior to processing and paraffin-embedding. Sections were cut and stained with hematoxylin and eosin. Additional immunohistochemical stains were performed by our in-house immunohistochemistry laboratory; a Ventana automated staining system was used according to the manufacturer's recommendations (Ventana Medical Systems, Tucson, AZ). The system is validated on a regular basis, and all stains were accompanied by appropriate negative and positive controls.

Address correspondence to:

Nils Lambrecht, MD, PhD, Pathology and Laboratory Medicine Service, Diagnostic and Molecular Medicine HCG, Long Beach Veterans Affairs, 5901 East 7th Street, Bldg 1, Rm 200M, Long Beach, CA 90822-5201; Phone: 562-826-8000; Fax: 562-826-5623; E-mail: Nils.Lambrecht2@va.gov.



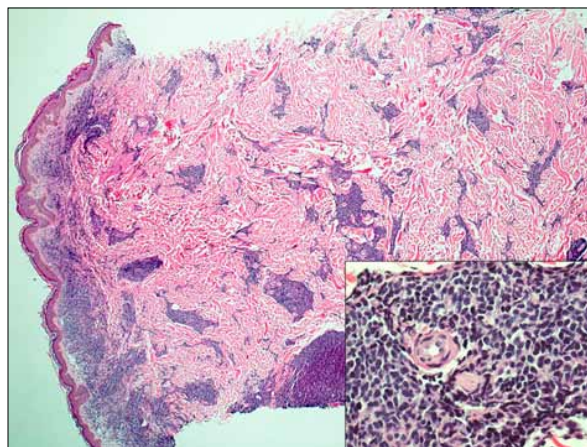
**Figure 1.** Top panel: Posterior scalp lesion 4 days before second chemotherapy (10/28/09). Bottom panel: Dramatic resolution of posterior scalp lesion at day 8 of second chemotherapy (11/10/09).

Bone marrow aspirates were prepared using Wright-Giemsa stain. A portion of the cervical lymph node biopsy was finely minced and submitted for flow cytometry in RPMI medium.

## Results

### *Skin Biopsy and Initial Bone Marrow Biopsy*

The punch biopsy of a violaceous lesion of the left arm from August 2008 showed superficial and deep perivascular and interstitial infiltrates of small- to intermediate-sized tumor cells, with a relatively high nuclear-to-cytoplasm ratio, and moderate amounts of eosinophilic cytoplasm (Figure 2).



**Figure 2.** Skin punch biopsy (hematoxylin and eosin stain, 8/2008) showing superficial lichenoid and deep perivascular neoplastic infiltrates by small-to-medium sized plasmacytoid neoplastic cells (20× magnification). Insert: High-power field of neoplastic cells surrounding dermal vessel and nerve (400× magnification).

All tumor cells stained positive with an antibody against BCL-2. Antibodies against CD45RO, CD3, CD5, and CD20 highlighted scattered normal lymphocytes admixed with tumor cells. Antibodies against CD10, CD23, cyclin D1, pancytokeratin (AE1/3), chromogranin, and synaptophysin did not label any cells.

In October 2008, sections of the bone marrow biopsy (Figure 3) showed a hypercellular marrow (70%) and numerous clusters of tumor cells with a similar morphology as seen in the skin biopsy. Additionally, the tumor cells stained positive with antibodies against CD4, CD56, and CD138.

### *Cervical Lymph Node Biopsy With Flow Cytometry*

At the end of October 2008, a subsequent biopsy of the cervical lymph node (Figure 4) showed effacement of the architecture by a diffuse infiltration of tumor cells with a similar morphology and identical immunohistochemical profiles (positive for CD4, CD56, and CD138) as seen in the bone marrow biopsy. As expected, the flow cytometry studies demonstrated a large population of cells expressing CD4, CD56, and CD123.

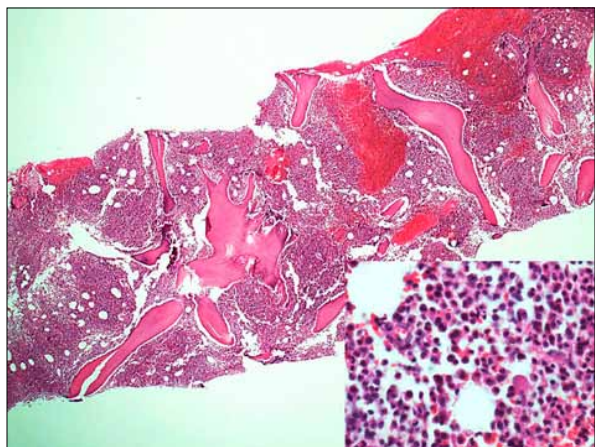
### *Repeat Bone Marrow Biopsy*

In August 2009, a repeated bone marrow biopsy showed a hypercellular marrow (80%), infiltrated by tumor cells with a similar morphology and immunohistochemical profile (positive for CD4, CD56, and CD138) as previously observed, which indicated relapse.

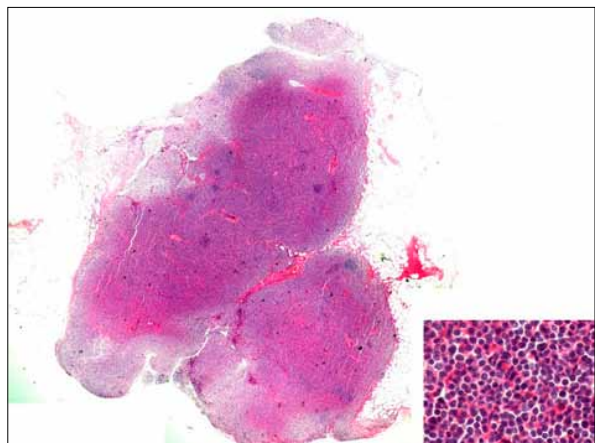
### *Autopsy*

Restricted (trunk only) autopsy was performed in November 2009. The cause of death was pulmonary and renal





**Figure 3.** Iliac crest (hematoxylin and eosin stain, 10/2008) showing diffuse infiltration of bone marrow by small- to medium-sized plasmacytoid neoplastic cells (20× magnification). Insert: High-power field of neoplastic cells (400× magnification).

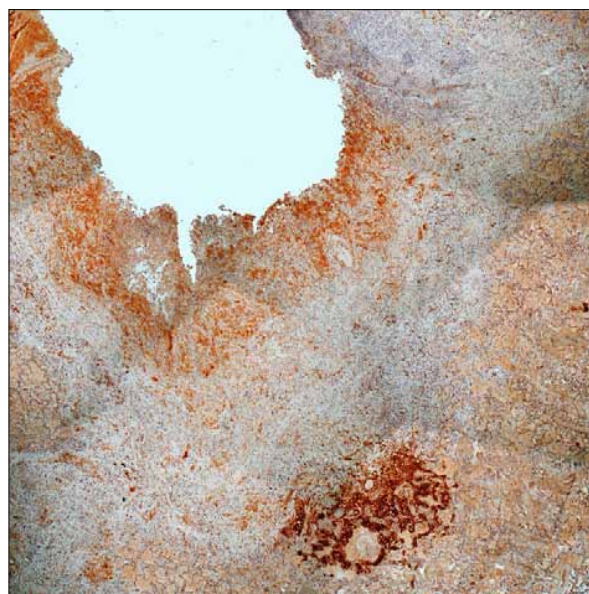


**Figure 4.** Cervical lymph node excision (hematoxylin and eosin stain, 10/2008) showing effacement of the entire node by small- to medium-sized plasmacytoid neoplastic cells (10× magnification). Insert: High-power field of neoplastic cells (600× magnification).

organ failure due to multiple massive acute hemorrhagic infarcts with disseminated intravascular coagulation. In addition, microscopic evaluation of the pulmonary infarct demonstrated rare clusters of CD56-positive, small- to intermediate-sized tumor cells in the areas of fibrosis adjacent to the infarct (Figure 5).

## Discussion

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare entity that was first described in 1994.<sup>1</sup> Morphologic features and CD4 expression initially suggested a T-cell lineage. Later, a natural-killer (NK) cell



**Figure 5.** Lung with hemorrhagic infarct (top panel hematoxylin and eosin stain, bottom panel CD56 immunostain, 11/2009) showing clusters of CD56-positive small- to medium-sized plasmacytoid neoplastic cells in peri-hemorrhagic fibrosis (20× magnification).

histogenesis was favored, based on CD56 expression. Thus, BPDCN was provisionally characterized as blastic NK-cell lymphoma in the 2001 World Health Organization (WHO) classification of pathology and genetics of tumors of hematopoietic and lymphoid tissues.<sup>2</sup> However, because CD56 is not an NK-cell-specific marker, and CD4 expression is not typical of NK-cell development, true NK-cell derivation for this tumor type was always considered problematic. Progress came with the delineation of the plasmacytoid dendritic cell, which

strongly expresses CD123. This finding, along with the recent demonstration that BPDCN also expressed CD123, provided a convincing histogenetic link.<sup>3</sup>

The incidence of this disease is rare, as it represents 0.7% of the data set of primary cutaneous lymphomas recorded by the French Study Group on Cutaneous Lymphomas for the past 10 years.<sup>4</sup> There is no defined treatment strategy, and therapeutic approaches vary widely, from irradiation in localized stages to myeloablative therapy. The initial response rate to treatment is high, with almost 70% complete remissions and 10% partial remissions. Unfortunately, similar to mantle cell lymphoma, most patients relapse and die of progressive disease.<sup>5</sup> A review of the literature suggests that acute lymphoblastic leukemia-like regimens are superior to lymphoma-like regimens.<sup>6</sup>

In addition, there are reports of improved survival after high-dose chemotherapy and radiotherapy followed by allogeneic stem cell transplantation when performed in first complete remission.<sup>7</sup> These include reports by Feuillard and colleagues, in which 2 of 3 patients (ages 6 and 29) treated with allogeneic bone marrow transplantation during complete remission were free of disease at 98 and 76 months, respectively, and reports by Cota and coauthors, in which 2 patients (ages 31 and 38) who were similarly treated were disease free at 21 and 9 months, respectively.<sup>8,9</sup>

The largest series reported by Reimer and associates reviewed the outcome of 6 new and 91 previously reported cases.<sup>7</sup> Treatment efficacy was compared among 4 groups of patients: those treated with regimens less intense than CHOP, those treated with CHOP and CHOP-like regimens, those treated with acute leukemia regimens, and 11 patients treated myeloablatively and with marrow transplantation during complete remission. The median overall survival was 13 months. Age over 60 was a negative prognostic factor, and there was no difference in survival between patients with systemic versus skin-limited BPDCN. Age-adjusted analysis showed a survivor benefit for patients treated with chemotherapy and radiotherapy followed by allogeneic bone marrow transplantation. However, the median age for this patient group was 28.5 years, and the authors concluded that the best treatment option for older patients remains unknown. Since most patients with BPDCN are in their seventh decade of life (median age, 67 years), the majority of patients are not eligible for transplantation.

To our knowledge, this is the first case of BPDCN treated with a chemotherapy regimen that is typically used for multiple myeloma. We chose the regimen of bortezomib, thalidomide, and dexamethasone because of the recently elucidated plasmacytoid dendritic cell origin of BPDCN. The patient had a very rapid response within days of initiating therapy. In fact, the rapidity of the patient's response exceeded that of his initial response to CHOP. This was unlikely due to collateral sensitivity because of prior CHOP exposure since the use of alkylators, anthracyclines, vinca alkaloids, and steroids fail to sensitize plasmacytic neoplasms to the subsequent use of bortezomib or thalidomide.<sup>10,11</sup> Although the patient eventually succumbed to massive hemorrhagic infarcts of lungs and kidneys, which may have been caused by rapid tumor lysis at sites of the disseminated disease, the therapeutic response, as measured by the relatively low abundance of tumor cells at the time of autopsy, provides a possible new regimen of less dose-dense bortezomib-thalidomide-dexamethasone for the treatment of this difficult-to-manage malignancy.

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# Review

## Blastic Plasmacytoid Dendritic Cell Neoplasm

John K. Lee, MD, and Gary Schiller, MD

*Division of Hematology/Oncology*

*Department of Medicine*

*David Geffen School of Medicine at UCLA*

*Los Angeles, California*

Shieh and colleagues<sup>1</sup> report an intriguing case of blastic plasmacytoid dendritic cell neoplasm (BPDCN) that was treated with novel therapy at the time of relapse. Initial treatment with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy induced a complete remission, but the patient rapidly relapsed off therapy. A novel salvage regimen of bortezomib (Velcade, Millennium Pharmaceuticals), thalidomide (Thalomid, Celgene), and dexamethasone was initiated, with rapid resolution of cutaneous disease. However, the patient succumbed to complications of BPDCN and associated treatment, presumably from an excessive therapeutic response leading to massive pulmonary hemorrhage. The patient's unfortunate clinical course highlights the aggressive, relapsing nature of this rare disease.

### Clinical Features

BPDCN was first described in 1994 in a patient with cutaneous disease, characterized by dermal infiltration of immature-appearing lymphoid cells expressing CD4 and CD56.<sup>2</sup> Since this clinical entity was first recognized, approximately 200 cases have been documented in the medical literature. BPDCN is rare; in a Spanish study,<sup>3</sup> it represented 0.76% of all acute myeloid leukemia, and 0.27% of all non-Hodgkin lymphoma. The male-to-female ratio is 3:1, and the median age at diagnosis is 65 years (although pediatric cases also occur infrequently).

Nearly all patients have solitary or multifocal cutaneous involvement that may appear as nodules, patch-plaques, or bruise-like areas. In half of all cases, skin lesions are the only manifestation of disease. Upon initial diagnosis, other sites of tumor infiltration include lymph

nodes, bone marrow, and blood. In one case series of 30 BPDCN patients,<sup>4</sup> 57% had skin-only disease; 21% had skin and lymph node disease; 11% had skin and bone marrow disease; 4% had skin, lymph node, and bone marrow disease; and 7% had leukemia at the time of diagnosis. The case reported by Shieh and colleagues<sup>1</sup> demonstrated diffuse involvement of the skin, lymph nodes, and bone marrow at presentation.

The prognosis for patients with BPDCN is poor, with a median survival of 14 months. Survival appears to be independent of the initial pattern of disease.<sup>5</sup> Diagnosis before the age of 40 years is a favorable prognostic factor,<sup>4</sup> although this may be confounded by differences in the intensity of therapy offered to younger versus older patients.<sup>6</sup>

### Histologic, Immunophenotypic, and Cytogenetic Features

Histologically, skin biopsy specimens of BPDCN reveal an infiltrate of cells that may range from small, lymphoid-appearing cells with smooth chromatin, to large, myeloblast-like cells with prominent nucleoli. Lymph nodes are involved in an interfollicular or diffuse pattern. Bone marrow involvement can be variable, from small nests to massive infiltration of tumor cells. Shieh and colleagues<sup>1</sup> provide representative images of hematoxylin and eosin (H&E) stains of skin, bone marrow, and lymph node biopsies in Figures 2, 3, and 4 of the case. On examination of peripheral blood or bone marrow smears, the tumor cells may exhibit microvacuoles that localize along the cell membrane ("string of pearls") and pseudopodia of agranular cytoplasm.

The characteristic immunophenotype of BPDCN is the expression of CD4 and CD56 without specific markers of T-cell, B-cell, or myelomonocytic lineage. The expression of CD123, an interleukin (IL)-3 receptor  $\alpha$ -chain, has also been demonstrated in more than 90% of BPDCNs.<sup>7</sup> Additional antigens that are expressed frequently in BPDCN include CD43, CD45, HLA-DR, T-cell leukemia 1 (TCL1), and cutaneous lymphocyte-associated antigen.

Chromosomal alterations in 5q, 6q, 9, 12p, 13q, and 15q are commonly found in patients with BPDCN.<sup>4</sup> In order to investigate these recurring genomic abnormalities, Jardin and coworkers performed array-based comparative genomic hybridization (CGH) in samples of 9 patients with BPDCN, and identified deletions of multiple tumor suppressor genes, including RB1, CDKN1B, CDKN2A, and TP53.<sup>8</sup> Wiesner and associates confirmed these genetic alterations at the translational level in 14 patients with BPDCN.<sup>9</sup> These findings suggest that dysregulation of the G1/S transition is critical to BPDCN tumorigenesis.

Address correspondence to:

Gary Schiller, MD, Center for Health Sciences, 10833 LeConte Avenue, Room 42-1212, Los Angeles, CA 90095; Fax: (310) 206-5511; E-mail: gschiller@mednet.ucla.edu.



## Cell Type of Origin

The early, evolving nomenclature of BPDCN reflected a limited understanding of disease histogenesis. BPDCN has previously been associated with T-cell, plasmacytoid monocyte, and NK-cell lineages, based empirically on morphology and cell surface antigens. More recent designations for this clinical entity have included agranular CD4-positive NK-cell leukemia, blastic NK-cell lymphoma, and agranular CD4-positive/CD56-positive hematodermic neoplasm.

The identification of CD123 expression in both BPDCN and plasmacytoid dendritic cells (pDC) ultimately suggested an immunophenotypic link.<sup>6</sup> pDCs are antigen presenting cells that exhibit a plasma cell-like morphology and localization. They are produced in the bone marrow, circulate in the blood (comprising fewer than 1% of total peripheral blood mononuclear cells), and infiltrate lymph nodes and mucosal sites when an immune response is activated.<sup>10,11</sup> BPDCN closely resembles at least one subset of pDCs in the shared expression of CD4, CD45, HLA-DR, CD56, and CD123.<sup>12</sup> Gene-expression profiling of BPDCN by Dijkman and colleagues also showed increased expression of various pDC-related genes, including TCL1a and IL3RA, as well as selective expression of Toll-like receptors TLR9 and TLR10.<sup>13</sup> Functional similarities between BPDCN and pDCs were identified by Chaperot and associates, with demonstrations of apoptotic rescue mediated by IL-3, induction of a Th2 phenotype with IL-3 and CD40L stimulation, and alpha interferon production after influenza virus exposure.<sup>14</sup>

With mounting evidence supporting the pDC histogenesis, the term *blastic plasmacytoid dendritic cell neoplasm* was introduced in 2008 by the World Health Organization.

## Treatment

No consensus exists about the optimal therapeutic management of BPDCN. The clinical course of BPDCN is characterized by initial responsiveness to various chemotherapeutic agents, or radiotherapy followed by relapse and progressive chemoresistance. Long-term remissions have rarely been reported.

The patient described by Shieh and colleagues<sup>1</sup> achieved a complete remission with 8 cycles of CHOP chemotherapy, but relapsed 3 months after discontinuing treatment. The overall response to initial treatment in a large case series by Reimer and associates was 80%, with nearly 70% of patients achieving complete remission.<sup>6</sup> However, only 20% of patients showed sustained remission at the last follow-up, with a median observation period of 16 months. There was a correlation between the

intensity of therapy and survival. In an age-adjusted evaluation, only allogeneic stem cell transplantation (SCT) in first complete remission showed superiority in overall survival compared to all other treatments.

Furthermore, in a retrospective analysis reported by Dalle and colleagues of 57 BPDCN patients registered in the French Study Group on Cutaneous Lymphoma, the mean overall survival for all patients undergoing transplant compared to those patients not treated via transplant was 31.3 months versus 12.8 months ( $P=.0018$ ).<sup>5</sup> The patients (mean age, 43.9 years) received induction therapy with an acute lymphocytic leukemia-type regimen, followed by allogeneic SCT in 9 patients and autologous SCT in 1 patient.

A small case series of German BPDCN patients presented by Dietrich and associates suggests that allogeneic SCT with reduced-intensity conditioning in elderly patients is practical, and may result in sustained remissions.<sup>15</sup> Of the 6 patients (median age, 67 years) reported, 4 underwent allogeneic SCT from unrelated donors. Two patients remain in remission 57 months and 16 months after transplant, whereas the other patients relapsed at 6 and 8 months after transplant.

Without aggressive therapy, outcomes are dismal. Prolonged remissions cannot be obtained with chemotherapy or radiotherapy alone. The best reported survival outcomes have been achieved in those who undergo allogeneic SCT after preparative regimens that are myeloablative (for younger patients) or reduced-intensity (for elderly patients). Unfortunately, the patient presented by Shieh and colleagues<sup>1</sup> relapsed while being evaluated for SCT, and died soon thereafter.

## Conclusion

BPDCN is a rare, aggressive malignancy derived from pDCs. BPDCN notably exhibits tropism for the skin, but also frequently involves lymph nodes, bone marrow, and blood. The diagnosis of BPDCN requires histologic identification of infiltrating or circulating tumor cells with characteristic CD4-positive/CD56-positive/CD123-positive immunophenotype. Chromosomal abnormalities are common in BPDCN, and contribute to cell cycle dysregulation at the G1/S transition, which may represent an important step in tumorigenesis.

No standard of care exists for the treatment of BPDCN, and the overall prognosis is poor. BPDCN may be sensitive to chemotherapy and radiotherapy initially, with the majority of patients achieving response. However, the disease inevitably relapses and becomes increasingly resistant to chemotherapy. The best outcomes have been reported in younger patients who undergo allogeneic SCT after myeloablative conditioning in first complete

remission. Elderly patients may also benefit from allogeneic SCT after reduced-intensity conditioning.

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