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Case report

Early relapse of Burkitt lymphoma heralded by a bone marrow necrosis and numb chin syndrome successfully treated with allogeneic stem cell transplantation

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ABSTRACT

The optimal salvage therapy for patients with relapsed Burkitt lymphoma is unknown. Bone marrow necrosis is an underreported (< 1% of bone marrow failures). Numb chin syndrome is another rare syndrome associated with aggressive malignancies. Survival of these syndromes is dictated by the underlying disease and is usually dismal. Our 35-year-old patient experienced an early relapse of Burkitt lymphoma accompanied by syndromes, achieved second complete remission and underwent allogeneic stem cell transplantation. He remains alive and well > 2 years after the transplant. To our knowledge, this is the longest reported survival of the two syndromes in the setting of BL relapse.

1. Case report

We present a case of a man who initially presented at age of 34 with complaints of cough, malaise, fever and bone pain, thrombocytopenia $35 \times 10^3/\mu L$, anemia (hematocrit 23.9%) and leukocytosis $13.7 \times 10^3/\mu L$ with 16% bands, but no other immature cells. Given his outdoor lifestyle and exposures an extensive infectious disease work up was performed including Lyme disease, Rocky Mountain Spotted Fever, anaplasmosis, babesiosis was negative. With worsening clinical status and LDH of 2730 IU/L the patient had a bone marrow (BM) biopsy performed. The bone marrow was inaspirable, however core biopsy revealed 100% cellularity and blastic-looking cells with high nuclear to cytoplasmic ratio, prominent nucleoli, basophilic cytoplasm and cytoplastic vacuoles (see Fig. 1A and B). Interphase fluorescence in situ hybridization (FISH) revealed 72/100 nuclei carried an IGH@-CMYC rearrangement further confirming a high-grade Burkitt lymphoma (BL), no rearrangements were seen using BCL6 and BCL2 probes. Polymerase chain reaction showed IgH monoclonal band. At the same time CT scan showed a $4.2 \times 4.9\ cm^2$ mass arising from the medial wall of the cecum, involving terminal ileum, an adjacent $5.0 \times 3.7\ cm^2$ lymphnode mass was seen in the mesentery with extensive soft tissue nodularities in the omentum. His cerebrospinal fluid showed normal protein and glucose, negative cytology (2 specimens × 2–3 mL) and flow (sensitivity 10^{-4}).

The patient began CODOX-M/IVAC with rituximab [2]. PET and BM after 2 cycles showed complete remission (CR) and this was confirmed 3 and 6 months later after he completed the full treatment course. There was no delay in administration of each cycle (average: 19 days, 16–21). Eight months after therapy completion he developed flu-like symptoms, WBC $9.1 \times 10^3/\mu L$, mild anemia and thrombocytopenia $23 \times 10^3/\mu L$, uric acid 4.7, LDH 1977 IU/L. CT scans were negative and BM showed relapse (see Fig. 1C and D). The patient complained of submental numbness, CSF sampling was negative × 3 by cytology and flow (2–3 mL each), MRI of the brain with focus on cranial nerves was negative for leptomeningeal involvement, his condition was concluded as numb chin syndrome (NCS). He received EPOCH-R with IT methotrexate 15 mg (on day 1) and IT cytarabine 100 mg (at least 72 h after MTX) [3]. After the first cycle the patient's marrow showed 80% cellularity and a large area of necrotic tumor cells occupying 60–70% of the total marrow space consistent with bone marrow necrosis (BMN), the remaining 30–40% of marrow comprised of viable tumor cells, which were intermediate in cell size with round nuclei, indistinct nucleoli and scant amount of cytoplasm (see

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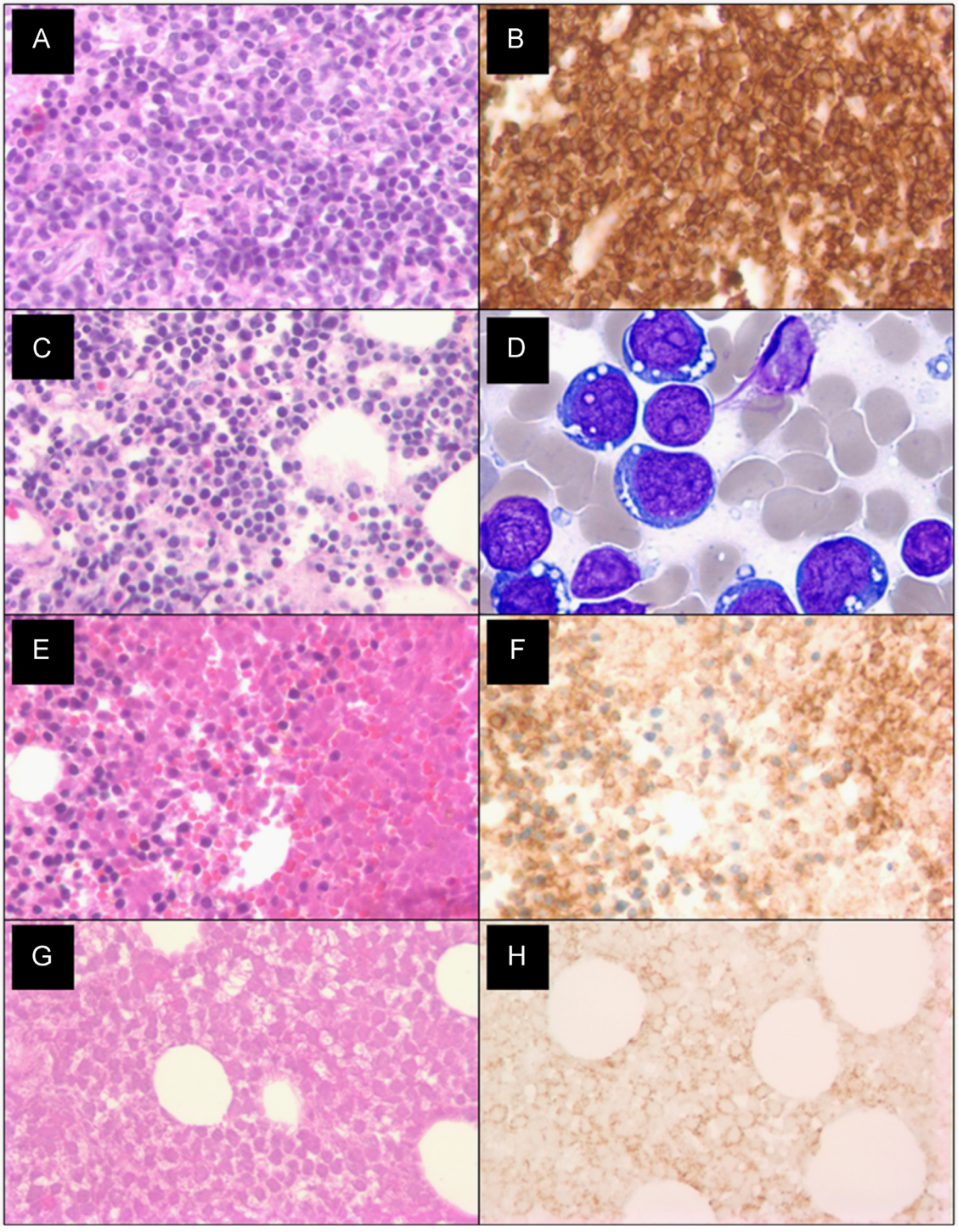

Fig. 1. (A) Bone marrow core biopsy showing 100% cellularity with diffuse Burkitt lymphoma infiltration effacing the normal marrow architecture, H&E stain. Majority of the cells were blastic-looking with high nuclear to cytoplasmic ratio, two to three prominent nucleoli, basophilic cytoplasm and cytoplastic vacuoles. Reticulin stain showed mild reticulin fibrosis. The neoplastic cells were negative for CD3, CD10, CD34, CD117, CD138, MPO, and TdT while they were strongly positive for CD20 (B) and positive for CD79a, BCL2, BCL6, PAX5, and Ki67 showed positivity in nearly 100% of cells. (C) Bone marrow biopsy showing Burkitt lymphoma infiltration, H&E stain. (D) Majority of the cells were blastic-looking with high nuclear to cytoplasmic ratio, two to three prominent nucleoli, basophilic cytoplasm and cytoplastic vacuoles. (E) Bone marrow core biopsy showing necrotic Burkitt lymphoma after first cycle of salvage chemotherapy. (F) Necrotic area with ghost outlines of intermediate-sized cells, which were positive for CD20. (G) Bone marrow core biopsy showing necrotic Burkitt lymphoma one year after allogeneic stem cell transplantation. 40% cellular marrow with maturing adequate trilineage hematopoiesis and 2/3 of the biopsy contained. (H) The necrotic area showed again many ghost outlines of intermediate-sized cells, which were positive for CD20, but negative for other markers CD3, PAX5, BCL-2, BCL-6, CD10, and Ki-67.

Fig. 1E and F). CD20 was strongly positive in both viable and necrotic tumor cells. Subsequent cycles were initiated at the first sign of hematological recovery (plts > 75,000/μL, ANC > 500/μL). Second CR was confirmed after second cycle (PET and BM). Aggressive prophylaxis with antibiotics, antifungals, antivirals, and against pneumocystis together with G-CSF were used. Fourth cycle was delayed by an episode of respiratory infection with parainfluenza 3, which was treated with IVIG (dose 500 mg/kg). After 6 cycles (average 16.6 days, 15–20) the patient underwent 10/10 HLA matched unrelated donor transplant (CMV: R+/D−) with

thiotepa/fludarabine/melphalan, posttransplant cyclophosphamide and sirolimus [4], which was tapered rapidly within 4 months. He remained asymptomatic and GVHD free at one year after his transplant: WBC $6.7 \times 10^3/\mu L$, HCT 37.9%, and platelets $260 \times 10^3/\mu L$. BM from the site where necrosis was present at relapse showed 40% cellular marrow with maturing adequate trilineage hematopoiesis and $\frac{2}{3}$ of the biopsy contained a necrotic area with many ghost outlines of intermediate-sized cells, which were positive for CD20, but negative for other markers (see Fig. 1G and H). The patient's counts and chimerism (> 97% donor BM and blood) were stable. For profound hypogammaglobulinemia and frequent respiratory infections he has received monthly IVIG. He is currently alive and well 2 years after his transplant. To our knowledge, this is the longest reported survival of BMN in setting of BL relapse.

2. Discussion

The optimal salvage strategy for BL patients with a partial remission or relapsed disease, is unknown. Combination salvage chemotherapy is usually attempted, but very few to no patients with BL achieve a meaningful response regardless of the chemotherapy agents used [1]. Autologous or allogeneic stem cell transplantation (ASCT or AlloSCT) represents a logical next step in consolidation of response; however, published data addressing high-dose therapy in BL are confounded by selection bias and the data is limited to subgroups of retrospective analyses [5–7], and case reports [8]. Chemosensitivity and disease status at the time of transplant determine the outcome. While clinical trial participation is warranted, due to time constrains this is very often not practical for patients and their physicians.

Given the presence of BMN an AlloSCT was chosen for our patient. BMN is a rare and poorly understood complication of aggressive hematological malignancies with dismal survival ranging from 1 to 4 months. Retrospective data associated upto 15% of BMNs with lymphoma [10]. Different sites were used for BM biopsies and we cannot confirm whether BMN was present before salvage therapy. We however confirmed that BMN was persistent at least one year posttransplant proving the point that bone marrow can undergo remodeling, but is a prolonged process [9]. PET scan and MRI were not helpful in identifying the extent of the BMN. Associations with bone marrow fibrosis were seen, but historically these were limited to patients with underlying myeloproliferative neoplasms [9,10]. We did not see any increase reticulin. The finding of persistent BMN represents a therapeutic dilemma. Successful use of rituximab has been previously reported for PTLD related BMN [11]. Rituximab was discussed with the patient, but not used as he remains clinically stable with normal counts and he requires IVIG replacement for frequent respiratory infections.

NCS is a rare syndrome. In case series of NCS 14–47% were associated with of lymphoproliferative disorders [reviewed in [12]]. Survival is usually dictated by the underlying disease and short in the setting of aggressive malignancies. Since NCS may be a manifestation of an underlying malignancy it has to be taken seriously. Though imaging and CSF studies were negative in our patient the specimens collected were not high volume and we treated the patient with prophylactic IT methotrexate and cytarabine. Residual NCS is still present > 2 years since initial presentation. We did not identify the actual etiology, but differential diagnosis includes impingement with lymphoma, BMN, previous exposure to chemotherapy with higher frequency among highly proliferating neoplasms [12].

Conflict of interest

None.

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