European Journal of Case Reports in Internal Medicine

Hypercalcaemia, Renal Dysfunction, Anaemia, Bone Disease (CRAB Criteria): A Case of Lymphoma

Balraj Singh[1], Pooja Gogia[2], Parminder Kaur[3], Nirmal Guragai[3], Michael Maroules[1]

[1] Hematology & Oncology Department, Saint Joseph's University Medical Center, Paterson, NJ, USA

[2] Internal Medicine Department, Saint Peter's University Hospital, New Brunswick, NJ, USA

[3] Cardiology Department, Saint Joseph's University Medical Center, Paterson, NJ, USA

Doi: 10.12890/2020_002140 - European Journal of Case Reports in Internal Medicine - © EFIM 2020

Received: 11/11/2020
Accepted: 29/11/2020
Published: 21/12/2020

How to cite this article: Singh B, Gogia P, Kaur P ,Guragai N, Maroules M. Hypercalcaemia, renal dysfunction, anaemia, bone disease (CRAB criteria): a case of lymphoma. *EJCRIM* 2020;**7**: doi:10.12890/2020_002140.

Conflicts of Interests: The Authors declare that there are no competing interests.

ABSTRACT

Calcium elevation, Renal dysfunction, Anaemia and Bone disease (CRAB criteria) are usually seen in multiple myeloma (MM). We report a unique case of lymphoma with all the features of CRAB criteria. We describe a 59-year-old patient who presented with confusion, severe back pain, fatigue and constipation and was found to have hypercalcaemia, kidney dysfunction, anaemia and multiple osteolytic lesions. Physical examination and imaging did not reveal any enlarged lymph nodes. Work-up for MM (serum protein electrophoresis, serum immunofixation, bone marrow biopsy) was negative. The patient was diagnosed with diffuse large B-cell lymphoma based on a pelvic mass biopsy. Hence, our case report suggests that CRAB criteria are not pathognomonic of MM and that in the appropriate clinical scenario, lymphoma is a possible diagnosis.

LEARNING POINTS

- The CRAB criteria consist of end-organ damage with hypercalcaemia, renal dysfunction, anaemia and bone involvement.
- The CRAB criteria are not pathognomonic of multiple myeloma, and in the appropriate clinical scenario, lymphoma is a possible diagnosis.
- Major mechanisms by which hypercalcaemia of malignancy can occur are tumour secretion of parathyroid hormone-related protein (PTHrP), osteolytic metastases with local release of cytokines, or tumour production of 1,25-dihydroxyvitamin D (calcitriol).

KEYWORDS

Hypercalcemia, anemia, osteolytic lesions, lymphoma, multiple myeloma

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common histological subtype of non-Hodgkin lymphoma (NHL), accounting for approximately 30–40% of NHL cases [1]. It is most prevalent in the elderly population and incidence increases with age. It is slightly more common in males [1]. Usual presenting signs and symptoms commonly include a rapidly growing mass; constitutional symptoms of fever, night sweats or weight loss; and/or in some patients signs and symptoms pertaining to organ involvement [1].

The diagnosis of multiple myeloma (MM) requires clonal bone marrow plasma cells ≥10% or biopsy-proven bony or soft tissue plasmacytoma, and end-organ damage suggested by increased plasma calcium level, renal insufficiency, anaemia and bone lesions (CRAB) [2, 3].

Herein, we report an unusual case of DLBCL fulfilling the CRAB criteria.

European Journal
of Case Reports in
Internal Medicine

CASE DESCRIPTION

We report the case of a 59-year-old woman with a medical history of diabetes mellitus and hypertension who presented to the emergency department for confusion. According to the patient's family, she had been having difficulty in walking and had been mostly confined to bed over the previous few weeks. She had experienced unquantifiable weight loss, poor appetite, constipation and severe back pain for the past 3 months. Vital signs on presentation were stable. The patient was oriented to self only. Physical examination revealed dry oral mucosa and diminished skin turgor. The cardiovascular, respiratory, neurological and gastrointestinal examination was unremarkable. The patient did not have any palpable lymphadenopathy, macroglossia, hepatomegaly or splenomegaly. Initial blood work revealed normocytic anaemia, an elevated white count with left shift, hypovolaemic hyponatraemia, hypokalaemia, metabolic alkalosis, elevated creatinine and hypercalcaemia. Laboratory results are shown in *Table 1*.

The patient was started on intravenous fluids and bisphosphonates pamidronate 90 mg IV for hypercalcaemia. A computed tomography (CT) scan of the head showed multiple lytic lesions. A skeletal survey was carried out and revealed multiple osteolytic foci in the skull, right clavicle, left humeral head, left iliac bone, left superior pubic ramus and bilateral femur. A bone scan showed increased uptake on the left femoral head and posteromedial portion of the right 10th rib (a corresponding rib fracture was noted on the CT scan). Our patient's alkaline phosphatase (ALP, a bone formation marker) was elevated at 237 U/l (reference range: 34–104 U/l), likely due to the bone healing process in the femoral head and 10th rib, and hence the increased uptake on the bone scan. The patient subsequently had serum protein electrophoresis with immune fixation studies which did not reveal any monoclonal paraproteins or light chains. However, the serum kappa lambda ratio was 3.59 (reference range: 0.2–1.65). The urine kappa lambda ratio was 49.91 (reference range 1.03–31.76), there was a urine protein electrophoresis M-spike of 6.4% (reference range: negative) and urine immunofixation was positive for kappa type Bence-Jones proteinuria.

CT scanning of the thorax, abdomen and pelvis revealed bilateral adrenal masses, liver masses, and extensive lytic osseous metastasis throughout the skeleton. Biopsy of the pelvic mass showed diffuse proliferation of large atypical lymphoid cells with a round to slightly irregular nuclear contour, and scanty to moderate amounts of cytoplasm (*Fig. 1*).

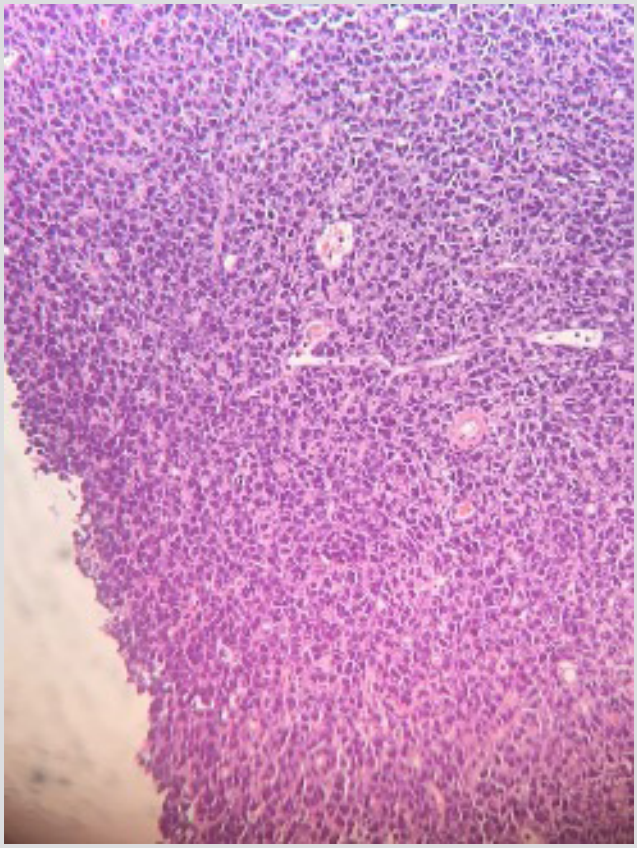

Figure 1. Diffuse proliferation of large atypical lymphoid cells with round to slightly irregular nuclear contours, and scanty to moderate amounts of cytoplasm (H&E ×200)

European Journal
of Case Reports in
Internal Medicine

Test	Value	Reference range
Haemoglobin	10.6 g/dl	12–16 g/dl
Haematocrit	30.8%	36–46%
White blood cells	$23.2\times10^3/mm^3$	$4.5\times103/mm^3$
Platelets	$374\times10^3/mm^3$	$140–440\times10^3/mm^3$
Mean corpuscular volume	86.8 fl	80–100 fl
Red cell distribution width	13.7%	0.5–16.5%
Neutrophils	94%	36–75%
Lymphocytes	1%	24–44%
Monocytes	0%	4–10%
Eosinophil	1%	0–5%
Basophil	0%	0–2%
Sodium	126 mEq/l	135–145 mEq/l
Potassium	2.8 mEq/l	3.5–5 mEq/l
Chloride	85 mEq/l	98–107 mEq/l
Bicarbonate	30 mEq/l	21–31 mEq/l
Blood glucose	143 mg/dl	70–110 mg/dl
Blood urea nitrogen	57 mg/dl	7–23 mg/dl
Creatinine	1.83 mg/dl	0.6–1.30 mg/dl
Calcium	17.0 mg/dl	8.6–10.3 mg/dl
Total protein	4.9 g/dl	6.4–8.4 g/dl
Albumin	2.9 g/dl	3.5–5.0 g/dl
Alkaline phosphatase	237 U/l	34–104 U/l
Aspartate aminotransferase	52 U/l	13–39 U/l
Alanine aminotransferase	68 U/l	7–52 U/l
Ferritin	1,416 ng/ml	12–300 ng/ml
Lactate dehydrogenase	527 U/l	140–271 U/l
Prothrombin time	13.3 seconds	12.2–14.9 seconds
International Normalized Ratio	1	0.9–1.1
Partial Thromboplastin time	20 seconds	21.3–35.1 seconds
Parathormone (PTH)	4.9 pg/ml	11.1–79.5 pg/ml
Vitamin D 25 OH	14.1 ng/ml	30–100 ng/ml
1,25 Dihydroxy vitamin D	36.8 pg/ml	19.9–79.3 pg/ml
Parathyroid hormone-related protein (PTHrP)	<2 pmol/l	<2 pmol/l
IgG	357 mg/dl	635–1471 mg/dl
IgM	24 mg/dl	40–280 mg/dl
IgA	118 mg/dl	66–433 mg/dl
Serum protein electrophoresis	Negative	Negative
Serum immune fixation	Negative	Negative
Kappa lambda ratio	3.59	0.2–1.65

Table 1. Laboratory evaluation summary

European Journal of Case Reports in Internal Medicine

On immunohistochemistry, the cells were diffusely strongly positive for CD20, BCL-2, BCL-6 (weak to moderate), PAX-5, MUM-1, MYC protein overexpression (80–90%), and the Ki-67 proliferation index was 90%. The large cells are negative for CD43, CD30, CD5, cyclin D1, CD138 and Pan cytokeratin. Bone marrow biopsy was negative for lymphoma involvement or a plasma cell disorder. These results supported a diagnosis of DLBCL with paraproteinaemia. Laboratory studies were negative for HIV and hepatitis B and C, and the echocardiogram was normal with an ejection fraction of 60%. Lumbar puncture was negative for lymphoma involvement. The patient was started on chemotherapy with R-EPOCH (rituximab, etoposide phosphate, prednisone, vincristine sulfate, cyclophosphamide and doxorubicin hydrochloride).

DISCUSSION

The presence of the CRAB criteria, which encompass end-organ damage with hypercalcaemia, renal dysfunction, anaemia and bone involvement, is considered highly suggestive of MM [2]. However, these symptoms are neither sensitive nor specific for MM. Individual CRAB features can be present in around 74% of patients with MM [4], and all four symptoms occur in only 30% of patients. Howsoever, there is only one case report in the literature of a patient with DLBCL presenting with CRAB features [3].

Although our patient had a slightly elevated serum kappa lambda ratio and urine studies positive for paraproteinaemia, production of a monoclonal paraprotein has been associated with various types of B-cell non-Hodgkin lymphomas [5]. Furthermore, our patient's bone marrow biopsy was negative for a plasma cell disorder, the immunoglobulin level was not elevated, serum protein electrophoresis and immunofixation was negative, and disease burden (adrenal, liver masses, bone disease) was consistent with the diagnosis of lymphoma. Paraproteinaemia has also been associated with AL amyloidosis [6]. However, the fact that our patient did not have macroglossia, hepatomegaly, splenomegaly or an abnormal coagulation profile (factor X deficiency), that haematoxylin and eosin staining on bone marrow was negative, and the pelvic mass biopsy and echo were normal, suggested against amyloidosis.

Hypercalcaemia is reported to occur around 20% of patients with malignancy at some point during their disease and particularly in advanced stages [7]. Hypercalcemia associated with malignancy is often symptomatic and is associated with a poor prognosis [7]. The most common cancers associated with hypercalcaemia in the USA are breast, renal and lung cancer and MM. In lymphomas, hypercalcaemia is uncommon at presentation but can occur with human T-lymphotropic virus type 1 (HTLV-1)-associated adult T-cell leukaemia-lymphoma and occasionally with transformed follicular lymphoma or DLBCL [8].

Major mechanisms by which hypercalcaemia of malignancy can occur are tumour secretion of parathyroid hormone-related protein (PTHrP), osteolytic metastases with local release of cytokines, or tumour production of 1,25-dihydroxyvitamin D (calcitriol). PTHrP or osteolytic metastases are usually the causes in solid tumours [9]. Increased production of 1,25-dihydroxyvitamin D (calcitriol) is the cause of almost all cases of hypercalcaemia in Hodgkin lymphoma and approximately one-third of cases in NHL as opposed to local osteolytic-induced hypercalcaemia that is thought to be the primary mechanism in MM. PTHrP-related hypercalcaemia has also been reported in patients with NHL on rare occasions [3]. In our patient, the cause of hypercalcaemia was likely the extensive osteolytic metastasis with local release of cytokines; laboratory results are shown in *Table 1*.

Acute kidney injury (AKI) is a common occurrence in patients with cancer. In general, the same aetiologies of AKI that occur in the general population can affect cancer patients; however, certain causes of AKI are specific to the cancer patient population.

Patients with cancer are at higher risk for infections, developing sepsis, tumour lysis syndrome and treatment-associated toxicities that increase the likelihood of AKI [10]. Malignant hypercalcaemia can also cause reduced response to the antidiuretic hormone which initially presents as the inability to concentrate urine. Subsequently, the renal blood flow and glomerular filtration rate diminish due to severe calcium-induced vasoconstriction.

Anaemia is a common feature in lymphoma patients. According to the European Cancer Anaemia Survey (ECAS), 39% of lymphoma patients were anaemic at the time they were enrolled in the survey. Anaemia has been shown to be an independent prognostic factor with a worse therapy outcome and increased mortality, and is associated with a higher stage [11]. The pathogenesis behind anaemia is likely bone marrow erythroid hypoplasia, shortened red cell survival, decreased erythropoietin production, bone marrow infiltration, hypersplenism from splenic involvement, and high inflammatory cytokine production by lymphoma cells [12].

Bone is a frequent site of metastasis in patients with solid tumours like breast and prostate cancer and such metastasis can cause significant morbidity and mortality for patients. Haematological malignancies do not frequently cause bone disease, although 70% of patients with MM present with bone involvement at diagnosis [2, 4]. Osteolytic lesions in lymphoma are found in 5–15% of cases, and hypercalcaemia is associated with lymphoma in 10% of cases. However, it is extremely rare (approximately 2%) for them to be the initial symptom of lymphoma [13]. Bone metastases can cause severe bone pain, pathological fractures, an oncological emergency like spinal cord compression, and derangements of calcium and phosphate homeostasis that can result in life-threatening hypercalcaemia [13]. Our patient had multiple extensive lytic lesions and fractures of the left femur head and rib.

European Journal of Case Reports in Internal Medicine

Our patient's alkaline phosphatase (ALP, a bone formation marker) was elevated at 237 U/l (reference range: 34–104 U/l) likely due to the healing process associated with fractures and hence the increased uptake on the bone scan. Thus, CRAB features can occur individually in DLBCL although synchronous presentation of all four features is very rare.

CONCLUSION

In conclusion, we report an unusual case of DLBCL presenting with CRAB criteria features. Our case adds to the limited literature available regarding lymphoma fulfilling CRAB criteria. Healthcare providers should have a high index of suspicion in the appropriate clinical scenario.

REFERENCES

1. Li S, Young KH, Medeiros LJ. Diffuse large B-cell lymphoma. *Pathology* 2018;**50**(1):74–87.
2. Rajkumar SV. Multiple myeloma: every year a new standard? *Hematol Oncol* 2019;**37**(Suppl 1):62–65.
3. Abdullah HMA, Ellithi M, Waqas Q, Cunningham A, Oliver T. Hypercalcaemia, renal dysfunction, anaemia and bone lesions (CRAB) do not always represent multiple myeloma: diffuse large B cell lymphoma presenting with CRAB symptoms in a 69-year-old man. *BMJ Case* Rep 2019;**12(**8):e229070.
4. Greenberg AJ, Rajkumar SV, Therneau TM, Singh PP, Dispenzieri A, Kumar SK. Relationship between initial clinical presentation and the molecular cytogenetic classification of myeloma. *Leukemia* 2014;**28**(2):398–403.
5. Dang M, Gajendra S, Goel S, Jha B, Sahni T, Sachdev R. Diffuse large B cell lymphoma with high M protein: an unusual finding. *Blood Res* 2015;**50**(1):61–62.
6. Cook L, Macdonald DHC. Management of paraproteinaemia. *Postgrad Med J* 2007;**83**(978):217–223.
7. Mirrakhimov AE. Hypercalcemia of malignancy: an update on pathogenesis and management. *N Am J Med Sci* 2015;**7**(11):483–493.
8. Conte GA, Harmon JS, Le ML, Sun X, Schuler JW, Levitt MJ, et al. Hypercalcemia in T-cell/histiocyte-rich large B-cell lymphoma: an unusual presentation of a rare disease and literature review. *World J Oncol* 2019;**10**(6):231–236.
9. Goldner W. Cancer-related hypercalcemia. *J Oncol Pract* 2016;**12**(5):426–432.
10. Rosner MH, Perazella MA. Acute kidney injury in the patient with cancer. *Kidney Res Clin Pract* 2019;**38**(3):295–308.
11. Ghosh J, Singh RK, Saxena R, Gupta R, Vivekanandan S, Sreenivas V, et al. Prevalence and aetiology of anaemia in lymphoid malignancies. *Natl Med J India* 2013;**26**(2):79–81.
12. Dicato M, Plawny L, Diederich M. Anemia in cancer. *Ann Oncol* 2010;**21** Suppl 7:vii167–72.
13. Tsuzuki S, Park SH, Eber MR, Peters CM, Shiozawa Y. Skeletal complications in cancer patients with bone metastases. *Int J Urol* 2016;**23**(10):825–832.