Bing-Neel Syndrome Successfully Managed by Ibrutinib: Case Report

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Keywords:
Waldenström macroglobulinemia, Bing-Neel syndrome, hyperviscosity, Splenomegaly, Ibrutinib

Abstract:
This abstract describes a case of Waldenström macroglobulinemia and Bing-Neel syndrome in a 33-year-old male patient who initially presented with bleeding diathesis, diffuse lymphadenopathy, and splenomegaly. Subsequently, the patient experienced progressive limb weakness and drowsiness. The diagnosis was confirmed, and the patient showed clinical, biochemical, and radiological responses to treatment with ibrutinib, an oral Bruton tyrosine kinase (BTK) inhibitor. This case highlights the rare occurrence of Bing-Neel syndrome as a complication of Waldenström macroglobulinemia and suggests the potential effectiveness of ibrutinib as a therapeutic option in such cases.

INTRODUCTION:

- Waldenström macroglobulinemia is an uncommon clinical condition characterized by the presence of clonal lymphoplasmacytic cells infiltrating the bone marrow and a monoclonal IgM gammopathy in the bloodstream. Hyperviscosity-related symptoms, including vision problems, headaches, dizziness, and neurological issues, can be present in up to 30% of Waldenström macroglobulinemia patients. It is typically diagnosed in older individuals, with the median age at diagnosis being 70 years, while less than 10 percent of patients are diagnosed under the age of 50 years.

- Bing-Neel syndrome is a rare complication of Waldenström macroglobulinemia where malignant lymphoplasmacytic cells infiltrate the central nervous system. It presents with diverse symptoms such as headaches, cognitive deficits, cranial nerve palsies, paresis, spinal cord dysfunction, and psychiatric symptoms. The optimal treatment for BNS is not standardized due to its rarity and limited literature.

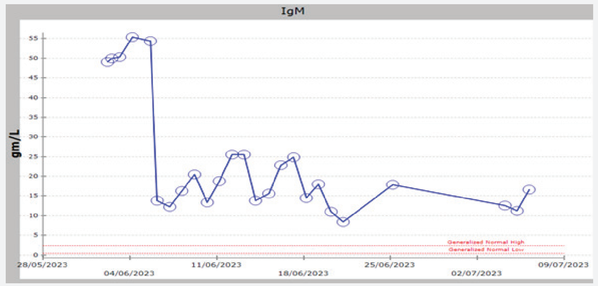
- The choice of systemic treatment should be individualized, considering factors such as patient condition, medical history, patient preference, and the physician's experience. Various treatment options, including intrathecal, intraventricular, targeted therapy, and systemic chemotherapy that has demonstrated or is likely to penetrate the blood-brain barrier, can be considered. However, one notable treatment option is the oral Bruton tyrosine kinase (BTK) inhibitor ibrutinib, which is approved in the United States and Europe for symptomatic Waldenström macroglobulinemia.

- Herein, we report a 33-year-old male patient who presented with bleeding diathesis, diffuse lymphadenopathy and splenomegaly. He developed abrupt progressive limb weakness and drowsiness. He has been diagnosed with Waldenstrom macroglobulinemia and Bing-Neel syndrome and he showed clinical, biochemical and radiological response to ibrutinib.

CASE PRESENTATION:

- Our patient is a 33-year-old Sudanese gentleman with no significant medical and surgical history. He noticed black tarry stool one week before presentation associated with five kilogram weight loss in two months duration, gum bleeding during tooth brush of almost three weeks duration and intermittent dizziness. Physical examination revealed splenomegaly with palpable bilateral axillary and inguinal lymphadenopathy. Initial blood work was remarkable for normocytic anemia with hemoglobin of 7.6 g/dl, MCV of 84.1 fl, INR of 1.6 and a protein gap of 83 g/l with total protein 105 g/l and albumin 22 g/l. Renal function, liver function and aPTT were unremarkable. Esophagogastroduodenoscopy showed evidence of mild gastritis and ultrasound abdomen confirmed hepatosplenomegaly. Peripheral smear showed increased rouleaux formation and serum protein electrophoresis revealed monoclonal IgM kappa in gamma region and IgM level was > 58.5 g/l.

FDG PET/CT scan showed hypermetabolic lymphadenopathy in the neck, axillae, chest, abdomen and pelvis along with splenomegaly with increased distal uptake, moderately hyperplastic bone marrow and small right lung nodule that is suggestive of lymphoproliferative disorder and lymphoma.(see image)
The patient underwent axillary lymph node and bone marrow biopsy. Next day he developed drowsiness, quadriplegia and urinary retention. Provisional diagnosis of hyperviscosity syndrome was made and he was started on pulse steroid and plasmapheresis. MRI head and spinal cord revealed an abnormal T2/FLAIR signal intensity involving bilateral cerebral deep white matter extending throughout basal ganglia and internal capsules to the brainstem and upper cervical cord up to C4-5 level (Image 1). Postcontrast images show diffuse supra/infratentorial sulcal and basal ganglia perivascular and pattern of enhancement involving the leptomeninges. Suspected perivascular enhancement also along the upper cervical cord (see image).
Weakness improved with repeated sessions of plasmapheresis. Meanwhile, axillary lymph node biopsy revealed malignant plasma cell proliferation (further details are needed from pathology report) and bone marrow biopsy confirmed involvement of bone marrow by a lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia. (further details are needed from pathology report). Patient was diagnosed with Waldenstrom macroglobulinemia along with Bing-Neel syndrome. CNS involvement which has been suggested by MRI findings was planned to be confirmed by lumbar puncture. However, it was difficult initially as patient was not cooperative and has bleeding diathesis. It was done few weeks after hospital admission and result showed 11 WBCs, 93% of them are lymphocytes and CSF protein of 0.85 gm/l. Patient was started on ibrutinib 560 mg daily and he showed clinical, biochemical and radiological improvement. Figure 1 showed level of IgM and its response to treatment.



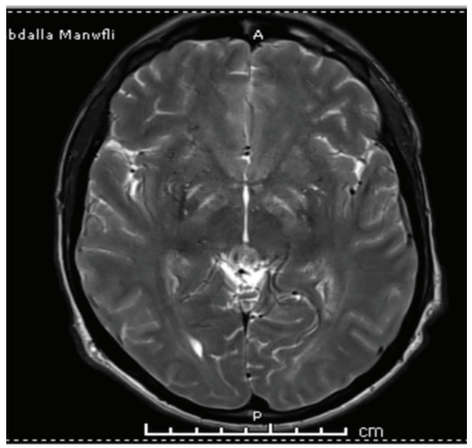


Image 1: Abnormal T2/FLAIR signal intensity involving bilateral cerebral deep white matter extending throughout basal ganglia and internal capsules to the brainstem and upper cervical cord up to C4-5 level.

He regained his functional status and follow up FDG PET/CT one month later showed improvement and resolution of hypermetabolic lymph nodes and regression of splenomegaly. His hospital course was complicated by central-line infection that treated effectively with antibiotics and then he was discharged and planned to continue ibrutinib along with rituximab as outpatient.

DISCUSSION:

- Bing-Neel syndrome can occur in individuals with Waldenström macroglobulinemia, even without systemic progression, and it can also be the first indication of both Bing-Neel syndrome and Waldenström macroglobulinemia, leading to a simultaneous diagnosis of both conditions. The exact incidence of Bing-Neel syndrome is uncertain; however, based on a retrospective cohort study involving 1,523 individuals diagnosed with Waldenström macroglobulinemia, only 13 patients (0.8%) were identified with Bing-Neel syndrome, indicating a very low prevalence.

- Treatment becomes more complex when Bing-Neel syndrome is diagnosed with Waldenström macroglobulinemia, as it necessitates addressing both systemic disease and the central nervous system involvement by selecting medications that can effectively penetrate the blood-brain barrier and target the underlying pathology. A multidisciplinary approach involving hematologists, neurologists, radiologists, pathologists, and other specialists is crucial for the optimal management of Bing-Neel syndrome. The optimal treatment for BNS is not standardized due to its rarity and limited literature. Several treatment options are available for Bing-Neel syndrome (BNS), including high-dose methotrexate (MTX), high-dose cytarabine, fludarabine, cladribine, bendamustine, and radiation therapy. Bruton's tyrosine kinase inhibitors such as ibrutinib, and acalabrutinib, are being used in the treatment of Waldenström macroglobulinemia.

- Multiple studies have shown that ibrutinib has the ability to cross the blood-brain barrier in patients with different B-cell malignancies, including Waldenström macroglobulinemia (WM). These studies have demonstrated that ibrutinib can have an impact on central nervous system (CNS) disease in lymphomas that are responsive to ibrutinib treatment. It is administered at a daily dose of 420 mg, which has shown effectiveness in treating WM. Furthermore, recent reports indicate that a dose of 560 mg, similar to the dosage used in Mantle cell lymphoma, is also effective in treating WM and possesses the ability to cross the blood-brain barrier. However, the optimal dosage and treatment schedule of ibrutinib for CNS disease are still not fully understood and require further clarification. A multicenter study investigated the effectiveness of ibrutinib in treating Bing-Neel syndrome. Twenty-eight BNS patients received ibrutinib monotherapy, with doses of 420 mg or 560 mg administered orally once daily. Within three months of therapy, 85% of patients experienced symptomatic improvements, 60% showed radiologic improvements, and 47% achieved clearance of the disease in the cerebrospinal fluid. The study reported promising survival rates, including a 2-year event-free survival rate of 80%, a 2-year ibrutinib survival rate of 81%, and a 5-year BNS survival rate of 86%.

- In our patient, using of ibrutinib at a daily dose of 560 mg resulted in clinical improvement of neurological symptoms and radiological improvement of lymphadenopathy and splenomegaly. This may provide additional evidence about the effectiveness of treatment for WM and Bing-Neel syndrome using Bruton's tyrosine kinase inhibitors.

DECLARATION:

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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ETHICAL DISCLOSURE:

The case approved by Hamad Medical Corporation Medical Research Center and the patient signed written informed consent for the publication of any potentially identifiable images or data included in this article.

AUTHORSHIP CONTRIBUTION:

The authors contributed equally to the manuscript.

Chronic Lymphocytic Leukemia with Central Nervous System Involvement Mimicking a Demyelinating Disease Treated Successfully with Ibrutinib.

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Running head: CLL with CNS involvement treated with ibrutinib

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Conflict of interest:
The authors declare that there is no conflict of interests regarding the publication of this paper.

Abstract:
Chronic lymphocytic leukemia (CLL) is a mature B cell neoplasm characterized by clonal proliferation of B lymphocytes in peripheral blood, bone marrow and lymphoid tissue. Leukemic involvement of the central nervous system (CNS) is rare with incidence less than 1%. In addition to the diagnostic challenge of CLL with CNS involvement (CNSi), no consensus exists about the optimal treatment. Herein, we describe a case of middle-aged male who presented with lymphocytosis and intramedullary lesion mimicking a demyelinating disorder. After comprehensive investigations, our patient is diagnosed with CLL Rai 0 with concurrent leukemic infiltration of the spinal cord. Patient was successfully managed with ibrutinib monotherapy.

INTRODUCTION:

- Chronic lymphocytic leukemia (CLL) is a mature B cell lymphoproliferative disorder characterized by a clonal B cell proliferation in the bone marrow, peripheral blood and the lymphoid tissues. Central nervous system (CNS) infiltration, though is rare, is the most common extramedullary site of CLL [1]. To the current knowledge, no risk factors of CLL with CNS involvement (CNSi) have been identified. Moreover, clinical manifestations are heterogeneous and non-specific [2]. There is no consensus agreement on the optimal treatment for CNSi in CLL patients.
  In this report, we aim to describe the diagnostic dilemma we faced in a case, who was otherwise healthy, presented with concurrent lymphocytosis and an intramedullary lesion and to review the literature on the optimal treatment for CNSi in CLL patients.

CASE PRESENTATION:

- A 55-year-old male referred from neurology department with right hand numbness, weakness and absolute lymphocytosis of 16 x 10^9/L. Physical examination was unremarkable apart from right upper limb weakness (4/5). Complete blood counts (CBC) showed: White blood cells (WBC) 28.5 X10^9/L, absolute lymphocyte counts (ALC) 16 x 10^9/L, hemoglobin level 15.1 g/dL and platelet count 254 x 10^9/L. Blood film morphology showed absolute mature lymphocytosis and few smudge cells. Peripheral blood flow cytometry showed clonal lymphocytosis expressing CD5+, CD23+, CD19+, CD200+, CD38+ and kappa light chain restriction and cytogenetic evaluation using fluorescent in situ hybridization (FISH) revealed 11q and 13q deletions. Magnetic resonance imaging (MRI) of the brain and neck demonstrated an intramedullary cord lesion located at C3 and C4 levels (figure 1A). The radiological findings were suggestive of a demyelinating process or less likely a neoplastic infiltration of the cord. Computed tomography (CT) scan of the abdomen and pelvis demonstrated multiply enlarged small supra and infra diaphragmatic lymph nodes (3.4 x 4.1 cm). The cerebrospinal fluid (CSF) examination showed a clear fluid with normal glucose, lactate dehydrogenase (LDH) and protein levels. Cytological examination of the CSF fluid demonstrated rare red blood cells and many small mature lymphocytes and flow cytometry revealed 15% clonal lymphocytes expressing CD5, CD19, CD23 and CD38 and kappa restriction. He was treated initially with triple intrathecal therapy (TIT) consisting of methotrexate, cytarabine and dexamethasone, however after three TIT the symptoms were persistent. Neuromyelitis optica was ruled out by negative aquaporin 4 membrane protein antibody. Patient was evaluated by neurologist who advised a trial of pulse steroid (1g/day) for five days duration because of the possibility of a demyelinating disorder. However, symptoms were persistent and worsening.

- Clinically, patient symptoms were progressing. Since CNSi by CLL is rare, we sought ruling out RT by PET/CT scan that showed mild FDG cord uptake (SUV Max 2.9) in the cervical area from C2 to C5. This finding decreased the possibility of RT. Final decision was to initiate therapy for CLL that can penetrate the blood-brain barrier (BBB). However, patient was reluctant to receive chemoimmunotherapy (CIT). Ibrutinib as a single agent was initiated in May 2019 at a dose of 420 mg/day. Patient showed clinical and radiological responses (figure 1B) after two months of commencing therapy with no toxicity.

DISCUSSION:

- CNS involvement in CLL (CNSi) is a rare complication. Strati and colleagues have reported 0.4% incidence of CNSi in CLL in 4174 CLL pts with no specific risk factor or clinical feature that can predict the CNSi [2]. CNSi might occur at any time during the course of CLL [1]. No correlation between CNSi and cytogenetic/molecular abnormality or Rai stage has been documented [1]. The clinical manifestations are heterogeneous, which include cranial nerve palsies, headache, cognitive decline, sensory and motor deficits. Lopez Da Silva has nicely reviewed the spectrum of CNS complications in CLL, ranging from infections, hemorrhagic, iatrogenic, other tumors to leukemia involvement [3], therefore careful evaluation of other differential diagnosis is warranted. At present, data is lacking about the prognostic significance of CNSi, however some reports indicating CNSi considered to be a high risk feature [4]. However, study by Strati et al., median overall survival (OS) of patients with CNSi were only 12 months [2] indicating a higher risk disease and shorter OS. On the contrary, the 5-year OS was higher in both treatment naïve and pre-treated patients with CNSi; 72% and 48% respectively (P = .006) as reported in more recent study by Wanquet et al. [5].

- As regard to management, no consensus exists on the optimal therapy [6]. Nevertheless, different treatment approaches reported in the literature in the form of case reports or case series, including CNS radiation, intrathecal chemotherapy, anthracycline based regimens, purine analogue based regimens and new targeted therapy including ibrutinib and venetoclax. It is crucial to diagnose and treat promptly CNSi CLL in order to improve outcomes.

- In a retrospective review of 78 cases of CLL with CNS involvement, intrathecal chemotherapy with or without systemic chemotherapy or CNS radiation was used in the majority of the cases [1]. The commonest intrathecal chemotherapy was methotrexate with or without cytarabine. The majority of the cases, which showed complete neurological remission, had intrathecal methotrexate [3], however responses were not durable.

- Other chemotherapeutic agents that cross the blood brain barrier include high-dose methotrexate and high-dose cytarabine and to a lesser extent fludarabine-based regimens with favorable activity against CLL. Fludarabine monotherapy demonstrated inconsistent outcome when used in CNSi with one report of complete neurological response [1]. Fludarabine has been used in combination with cyclophosphamide and rituximab with and without intrathecal chemotherapy in 9 pts achieving high response rate (9/9 pts, 100%) [5], bendamustine is an alkylating agent with purine analogue component and has been used in CLL.

- Dasatinib, a BCR-ABL and SRC-tyrosine kinase inhibitor, have shown a long-lasting complete remission when used in a case of primary CNS CLL who experienced a relapse after 2 lines of chemotherapy.

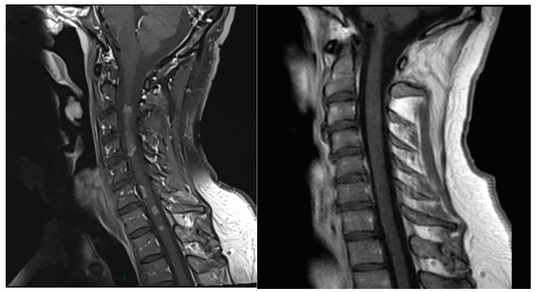
- Although, intrathecal rituximab is found to be safe and modestly effective in treatment of refractory primary CNS lymphoma, no report about its role in CNSi.

- Recently, ibrutinib with or without intrathecal chemotherapy demonstrated complete neurological response in three out of sex patients with CNSi and partial neurological response in the remaining based on a retrospective study. (blood j).

- Finally, venetoclax, a selective BCL2 inhibitor, demonstrated a promising result in CNSi when given with IT chemotherapy for a relapsing patient with CLL, who was heavily pretreated with chemoimmunotherapy and relapsed post-ibrutinib+IT. In the same case, CSF clearance achieved one month only after venetoclax initiation.

KEY CLINICAL MESSAGE:

- Though is extremely rare, leukemic infiltration of the CNS should be considered in the differential diagnosis of any neurological complaint in patients with CLL. Our report supports the previously published data about the efficacy of ibrutinib in treatment of patients with CNSi.



Lopez	1 pt	CNS CLL	IT MTX + arac + CHOP	CR	3 mon	Alive		
Elliot	1 pt	CNSi CLL	Fludarabine single x 6	CR	6 mon	Alive		
popla	1 pt	CNSi CLL	Chemo + IT MTX	Clinical improvement	6 mon	Died	Respi sepsis	Procarbazine CCNU DEXA Kuwa
kuwa	1 pt	CNSi CLL	TIT	Clinical imp	3 mon	Died	Resp sepsis	
hanse	5 pts / 129 pts	CNSi CLL	IT chemo +/- RT or chlorambucil/CHOP	Clinical imp	23+ mons	4 Alive 1 Died	CNSi progression	3 ch 1 CHOP No correlation BW outcome and CNSi : Rai/WBC

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Management of AL Amyloidosis at a South African State Hospital

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INTRODUCTION:

Amyloidosis is an uncommon cause of intrinsic renal disease. However, the most common renal presentation is nephrotic syndrome. Renal manifestations of systemic amyloidosis are most frequently seen either in the setting of chronic inflammation (AA amyloidosis), or plasma cell dyscrasias (AL amyloidosis). Without treatment, amyloidosis is associated significant morbidity and mortality. Those patients with kidney disease tend to progress rapidly to end-stage renal disease (ESRD) if untreated.

CASE REPORT:

- A 60-year-old Caucasian male presented to his general practitioner in September 2022 with pedal oedema. In addition, he reported a metallic taste in his mouth, experienced nausea, loss of appetite and weight loss of 12kg over the preceding 6 months. He also reported episodic back pain, dizziness, and syncopal episodes.

The patient has a significant smoking history of 45 pack years.

He was commenced on furosemide 40mg twice daily to relieve the oedema. It was also found that patient had nephrotic range proteinuria, 5g/day and in discussion with a nephrologist was commenced on a trial of corticosteroids. This was weaned off and stopped.
He was subsequently referred to the nephrologist for a renal biopsy. The full blood count (FBC) revealed a polycythaemia, with haemoglobin value of 18.1g/dL and haematocrit 0.526 L/L. He had a white cell count of WCC 19.35 X 10^9/L and a platelet count of 346 X 10^9/L.
His biochemistry results at presentation

Sodium	139 mmol/L
Potassium	5.1 mmol/L
Bicarbonate	27 mmol/L
Urea	5.1 mmol/L
Creatinine	96 mmol/L
Corrected calcium	2.29 mmol/L
Albumin	19g/L
LDH	487 U/L
Iron	14
Transferrin	1.66
% Saturation	34
Ferritin	619
Vitamin B12 and folate	Normal

The patient underwent a venesection and a renal biopsy was performed.

Renal biopsy
Amyloid deposition in the glomeruli, salmon pink in colour on Congo Red stains. Not enough tissue/ funds to submit for immunofluorescence.

Unfortunately, the patient could not afford the cost of further private health care and was referred to a state facility for further investigations and medical care.
The results of the investigations performed is shown below:

Bone marrow aspirate and trephine
Aspirate
Active trilineage haematopoiesis with serial maturation in different cell lineages.
Trephine
Plasma cells early seen with interstitial distribution. Small area of monomorphic, small mature cells resembling a lymphoid aggregate. No amyloid deposition. Plasma cells not increased - 3% of nucleated cells.

Flow cytometry on bone marrow aspirate
1.71% clonal plasma cells with lambda light chain restriction identified. In keeping with plasma cell dyscrasia.

Skeletal survey	Degenerative changes no lytic lesions

Positron Emission Tomography : 5 May 2023
Physiological distribution of tracer in the brain, heart, liver, spleen, bone marrow and kidneys. Head and Neck: No pathological uptake seen in the brain, head and neck. Thorax: No pathological uptake seen in the lungs and mediastinum. Abdomen and Pelvis: No pathological uptake seen. Musculoskeletal: No pathological uptake seen in the bones and soft tissue. PET/CT Conclusion There is no convincing of metabolically active disease.

Ultrasound of the kidneys and abdomen
Liver is enlarged in size (16.4 cm) with normal echopattern. No focal lesions or dilated intrahepatic ducts noted. Normal portal vein. The gallbladder is well distended. No calculi or wall thickening. The pancreas is normal. No focal lesions or pancreatic duct dilatation. The spleen is normal in size (10.4 cm) and echopattern and no focal lesions are noted. Both kidneys are normal in size (Rt: 11.6 cm, Lt: 11.6 cm) and echopattern with good corticomedullary differentiation. No evidence of hydronephrosis, hydroureter or perin ephric collections. No ascites.

Metabolic screening showed the patient to have dyslipidemia and a normal glucose tolerance test. Viral testing for HIV, hepatitis B and C screen as well as an antinuclear antibody screen was negative. The thyroid function test and Pro BNP were normal.

Serum protein electrophoresis	**3 April 2023**
Alpha-1-Globulins	2
Beta-1-Globulin	6
Beta-2-Globulin	2
Gamma Globulins	8
Paraprotein	2g/L (early gamma region)
Immune fixation	IgA Lambda. No immune paresis

Beta 2 microglobulin	2.7
Serum free light chains	Increased lambda light chains: 116. Lambda/kappa ratio low 0.1 (low)

17 May 2023 Protein/Creatinine Ratio	1.076 H

The Patient Was Referred to Our Centre in June 2023.

Patient reported paresthesia of both feet and legs.

CLINICAL EXAMINATION FINDINGS:

Performance status: ECOG2
Initial blood pressure 137/92 mmHg and pulse rate of 101. A postural drop in blood pressure was noted at 1 minute - BP 116/74 mmHg and at 3 minutes-110/73 mmHg .
He was afebrile. Respiratory rate: 14/min
General examination findings: Livedo reticularis. Bilateral moderate pedal oedema.
No lymphadenopathy
Oral cavity: Macroglossia. Dental caries noted.
Cardiovascular system: Normal heart sounds. No murmurs. No bruits
Chest: Hyperinflated. No crackles or wheezes
Abdomen: Soft; normal bowel sounds. No hepatosplenomegaly
Calves: Soft
Central nervous system: No abnormalities

MANAGEMENT:

Commenced CyBorD Regimen on 11 July 2023 with prophylactic acyclovir.
- Bortezomib mg SC once per day on days 1, 8, 15, 22
- Dexamethasone 40mg PO once per day on days 1, 8, 15, 22
- Cyclophosphamide 650mg PO once per day on days 1, 8, 15, 22

After 2.5 cycles of CyBorD, the patient reports feeling better.

The table below illustrates the response to therapy biochemically.

	10 October 2023
Alpha-1-Globulins	2
Beta-1-Globulin	4
Beta-2-Globulin	2
Gamma Globulins	4
Paraprotein	< 1 (early gamma)
Protein/Creatinine Ratio	0.891

Following 4 cycles of CyBorD, we plan to proceed to autologous stem cell harvest with etoposide and G-CSF. Thereafter Mel-200 and stem cell re-infusion.

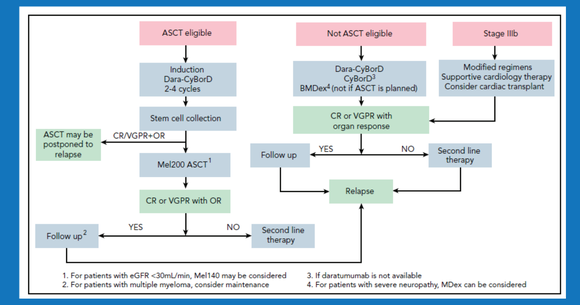
DISCUSSION:

Amyloidosis may affect different organs and clinical manifestations are deceitful and often recognized at an irreversible stage[1]. This case highlights the importance of creating awareness amongst primary health care practitioners to facilitate early referrals for further investigations prior to the onset of advanced end organ damage. The table below entitled “Presymptomatic hints, symptoms, and signs leading to the diagnosis of AL amyloidosis” is a useful reference, to help guide clinicians.[1]

Presymptomatic	Symptomatic		
	Organ involved	**Symptoms**	**Signs**
Increased markers of possible amyloid organ involvement: • Heart: NT-proBNP • Kidney: Albuminuria • Liver: Alkaline phosphatase Monitored during follow-up of MGUS patients and particularly in those with abnormal FLC ratio, and LC propensity to form amyloid (glycosylated κ-LCs, use of LC genes IGLV6-57, IGLV2-14, IGLV1-44, and LCs identified by machine learning algorithm)	Heart	Reduced exercise tolerance Dyspnea at rest or exertion Fatigue Syncope Angina	Lower extremity edema Pleural effusions Jugular vein distension Arrhythmia Thickened ventricular walls and low voltages on ECG
	Kidney	Loss of appetite Fatigue and weakness	Lower extremity edema Anasarca
	Soft tissues	Jaw or buttock claudication Carpal tunnel (often bilateral) Dysarthria	Periorbital (upper body) purpura Macroglossia Nail dystrophy Shoulder pad Arthropathy Myopathy
	Peripheral nervous system including autonomic nervous system	Length dependent sensory-motor neuropathy Lipothymia Taste alterations Early satiety	Orthostatic hypotension Intestinal dysmotility Erectile dysfunction Voiding dysfunction
	Liver	Right upper quadrant tendemess Jaundice Early satiety	Hepatomegaly Weight loss
	Gastrointestinal tract	Abdominal discomfort	Malabsorption Gastrointestinal bleeding Diarrhea Weight loss

Palladini G, Merlini G. How I treat AL Amyloidosis. Blood 2022. 139(19)

Treatment should be tailored according to the organ involved and clonal characteristics. The combination of daratumumab and bortezomib combination is considered the standard-of-care for newly diagnosed patients with AL amyloidosis.[1] (see algorithm below). This combination has the capability of inducing rapid and deep responses, however in the resource constrained health care settings, the use of this combination may not be possible.



Palladini G, Merlini G. How I treat AL Amyloidosis. Blood 2022. 139(19)

CyBorD followed autologous stem cell transplant remains a viable option in transplant eligible patients with AL amyloidosis in the South African context.

CONCLUSION :

Amyloidosis is an uncommon cause of kidney disease and typically presents with nephrotic syndrome. It is therefore important for health care practitioners to consider this as a potential cause of nephrotic syndrome once the more common causes have been reliably excluded.

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A Case Report of Chronic Lymphocytic Leukemia in a Young Black South African Man

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INTRODUCTION:

Chronic Lymphocytic Leukaemia (CLL) is an acquired clonal lymphoproliferative disorder leading to an accumulation of mature B lymphocytes which are functionally incompetent. CLL is relatively rare in South Africa compared to the western world, however it appears to have an aggressive clinical course in the black South African population and presents at a younger age.

CASE REPORT:

- A 39-year-old black South African male with a background of HIV and hepatitis B co-infections on anti-viral treatment and virologically suppressed, presents with a 4-month history of significant bilateral lymphadenopathy and constitutional symptoms. Physical examination revealed a massive splenomegaly. An excision biopsy confirmed the diagnosis of CLL. Molecular testing demonstrated a 17p deletion in 85% of cells as the sole abnormality. Routine blood analysis, flow cytometry, bone marrow biopsy and a staging CT scan were performed as part of the work up. He was classified as Rai stage IV.
  Full blood count (FBC) revealed a leukocytosis of 68.07 x 10^9/L, a severe anaemia of 4.9 g/dL, a thrombocytopenia of 29 x 10^9/L and an absolute lymphocyte count of 64.67 x 10^9/L. Although a direct anti-globulin test was not performed at the time, it was suspected that the anaemia may have been immune-mediated. The flow cytometry revealed a population of cells which expressed CD5+, CD19+, CD23+, dim CD20+, CD43+, CD79b-, FMC7- and surface lambda light chain restriction in keeping with a CLL phenotype. Symptomatic anaemia and sepsis complicated his multiple admissions.
  The treatment options in our setting are limited due to economic constraints. We elected not to treat him with FCR (fludarabine, cyclophosphamide and rituximab) due to severe and recurrent infections, as well as his poor performance status. We opted commence him on R-CVP (rituximab, cyclophosphamide, vincristine and prednisone) in an attempt to reduce the disease burden. We concurrently provided support with blood products and antibiotics. He has remained transfusion dependent. The suspected auto-immune haemolytic anaemia did not respond to high dose prednisone therapy. Intravenous immunoglobulin was administered in view of the ongoing infections.

DISCUSSION:

Over the last few decades CLL therapy has undergone many changes. The treatment landscape of CLL in South Africa remains challenging due to the limited access to effective oral targeted therapies such as Bruton's Tyrosine Kinase (BTK) inhibitors and venetoclax, in the state-funded healthcare system. Selecting the correct treatment for the patient requires consideration of the patient's co-morbidities, disease characteristics and prior therapies. Patients with TP53 disruptions have a shorter progression free survival and overall survival when treated with standard immunochemotherapy regimens such as FCR. In view of the 17p deletion the ideal upfront therapy would be either a BTK inhibitor alone or venetoclax plus an anti-CD20 monoclonal antibody. We are hoping to start zanubrutinib pending a special motivation on a compassionate use programme. Zanubrutinib is a second generation covalent BTK inhibitor with higher specificity and less off-target inhibition than ibrutinib.

CONCLUSION:

In conclusion we report a case of CLL in a young black man with a 17p deletion. This case demonstrates the importance of having access to novel therapies and further highlights the difficulties we have in treating CLL in a resource limited setting.

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Adolescents and Young adults with Multiple Myeloma , Kuwait Experience

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Background

Multiple myeloma MM is an incurable plasma cell malignancy with a median age of 65 years at diagnosis worldwide, a small number of publications were focused on young adult Multiple myeloma MM with special characteristics and clinical outcomes.

Objectives

To evaluate the incidence of MM among adolescent and young adults (AYA) in Kuwait aged 40 and below. Also, to describe the clinical characteristics, high risk features and treatment outcomes at the Kuwait Cancer Control Centre (KCCC).

Materials & Methods

Adolescent and Young adult Multiple Myeloma were defined as onset of MM at the age of 40 or below, In Kuwait a total number of 340 patients were diagnosed by multiple myeloma from 2015 till 2022 , We collected data retrospectively from the hematological malignancy registry at KCCC and looked at AYA patients (pts) with a confirmed diagnosis of Multiple myeloma at our centre from 2015 till 2022, we looked at age of onset, gender, nationality, year of myeloma diagnosis, presence of extramedullary disease, International Staging System score (ISS score), cytogenetic aberrations, induction therapy, receipts of auto-transplant and maintenance therapy.

Tables

Table 1: Patient Demographics

SEX		Nationality		Extra medullary		ASCT		Maintenance		Relapses			FISH				
M	F	K	NK	Y	N	Y	NA	NA	Y	Y	No	NA	t(11.14)	+1q	t(14,16)	Del 17p	t(4,14)
10	1	3	8	4	7	10	1	1	10	2	7	2	0	1	0	0	0

M:Male, F:Female, K:Kuwaiti, NK:Non-Kuwaitii, Y:yes, NA:not available, ASCT:Auto Stem Cell Transplantation

Table 2:Age at diagnosis

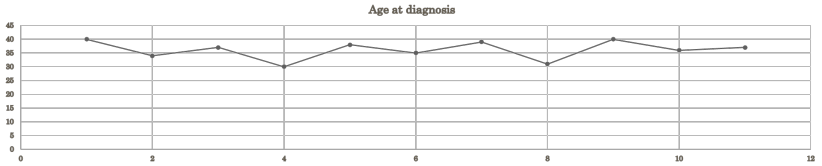


Table 3: ISS Staging

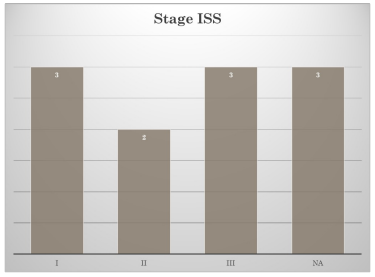
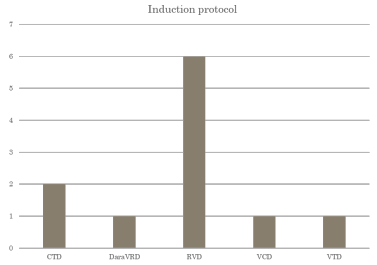


Table 4: Protocol



Discussion

From 2015 till 2022, 340 pts were diagnosed with MM in Kuwait, eleven pts were found 40 years old or younger, only one was female pt, the median age was 35 years old, around a third were Kuwaiti, 73% were non-Kuwaiti of middle eastern background, 4 pts were found to have extramedullary disease at diagnosis, with advanced stage ISS III found in 3/9 pts. One pt was found with 1Q gain and the rest of the 10 patients were with negative del17p, t(4,14), t(14,16), gain1q and t(11,14). Of note, interphase FISH cytogenetic is not done with CD138 selection. Six pts were treated with RVD induction (lenalidomide, Velcade, Dexamethasone), two pts treated by CTD (cyclophosphamide, Thalidomide, dexamethasone), one pt treated by VCD, one pt treated by Daratumumab RVD, and one patient treated by VTD. Overall response rate (ORR) was 90.9%, (10/11) responded patients proceeded to HDCT/ASCT and all these patients went on maintenance post-transplant, two patients were lost to follow up while 9 patients still under follow up, median follow up 33 months, one pt had a relapse after transplant.

Conclusion

MM is an uncommon disease among AYA in Kuwait (3.2%) of all myeloma patients, with favorable durable responses in this group of pts.

References

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Keywords

MM: Multiple Myeloma
HDCT:High dose Chemotherapy ,
ASCTAutologous Stem Cell Transplantation.

Title

Daratumumab effectiveness in heavily pretreated immune thrombocytopenia patients: a Case Series

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Introduction

Immune Thrombocytopenia is an acquired immune mediated peripheral destruction of platelets. It is a relatively common disease, with incidence 3.9 per 100,000 per year. Treatment is generally indicated when the platelet count is < 30 X 10^9 /L. First line treatment of immune thrombocytopenia is corticosteroids. Approximately 80% of adult patients with ITP have treatment failure with corticosteroids or become dependent on them and require second-line therapy. Second-line and subsequent therapies includes Rituximab, thrombopoietin receptor agonists, splenectomy, fostamatinib, and other immunosuppressive therapies. The response rate of second and subsequent therapies is variable, and some patients relapse after multiple treatment lines.

Daratumumab is an anti-CD-38 monoclonal antibody which targets plasma cells and primarily used for the treatment of multiple myeloma. Plasma cells are responsible for the production of antiplatelet antibodies. Multiple case series and case reports has showed that daratumumab is effective for the treatment of immune thrombocytopenia and autoimmune cytopenia. Here, we report our center experience with the use of daratumumab in the treatment of heavily pretreated immune thrombocytopenia patients.

Methodolgy

We conducted a review of all patients with the diagnosis of immune thrombocytopenia who received daratumumab in our center. Informed consent has been obtained from all patients. The study received institutional review board approval. The dose of daratumumab was 16 mg/kg and it is uniform across all patients. Number and frequency of doses varied and were based on physician's discretion as there are no standards. All patients received paracetamol, diphenhydramine and steroids (dexamethasone, hydrocortisone or methylprednisolone) as pre-medications. We followed the International Working Group(IWG) definitions for response assessment, where "complete response, CR" is defined as platelet count >100 X 10^9/L and no bleeding symptoms, "response, R" is defined as platelet count > 30 X 10^9/L or at least a twofold increase from the baseline count and no bleeding symptoms and "no response,NR" is defined as platelet count < 30 X 10^9/L, < a twofold increase from the baseline count, or presence of bleeding symptoms.

Results

Four patients received daratumumab for immune thrombocytopenia. The median patients age is 27(Range, 17-49) . The median number of previous therapies is 6 (Range, 5-8). One patient have had previous splenectomy (#3). At the time of starting daratumumab, the median disease duration was 6 years (Range, 4-12).

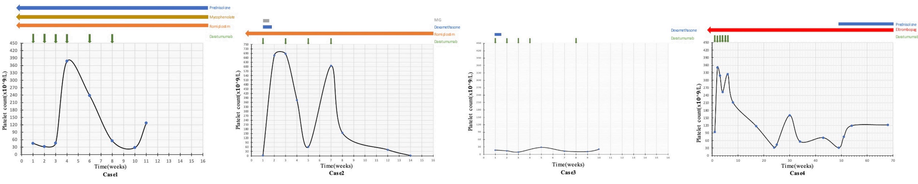
Three patients (#1, #2, #4) achieved complete response. Median time to response was 2 weeks (Range, 1-4 weeks). Duration of response was 10, 14 and 68 weeks, respectively. Patient #1 and #2 have relapsed while patient #4 has ongoing complete response. patient #3 had no response. Patient number #4 have had a drop in platelet count to 31 x10^9/L at week 49, for which she was started on tapering dose of steroids.

There was no major adverse events except for mild infusion reactions (patient #1, #2, #4) that has resolved with manipulation of infusion rate and supportive measures(steroids/antihistamines). There was no hematological toxicity and no infections.

Table 1: characteristics and outcome of patients.

Patient number	Age/Sex	Other underlying diseases	Previous splenectomy	Previous therapy	Number of Daratumumab infusions	Treatments given with daratumumab	Response	Duration of response (weeks)	Time to response (weeks)	Relapse
1	17/Male	None	No	Steroids(CR) Rituximab(NR) Eltrombopag(CR) Romiplostim(CR) Mycophenolate (NR)	6	Romiplostim Mycophenolate Prednisolone	CR	10	4	Yes
2	23/Female	Vitamin D deficiency Iron deficiency anemia	No	Steroids(CR) IVIG(CR) Rituximab(CR) Eltrombopag(NR) Romiplostim(CR) Azathioprine(NR)	4	Dexamethasone Pulse IVIG(for 2 days) Romiplostim	CR	14	1	Yes
3	31/Female	Iron deficiency anemia	Yes	Steroids(NR) IVIG(NR) Rituximab(NR) Splenectomy(NR) Eltrombopag(CR) Romiplostim(NR) Avatrombopag(NR) Azathioprine(NR)	5	Dexamethasone pulse	NR	NR	NR	NR
4	49/Female	Vitamin B12 deficiency Iron deficiency anemia Vitamin D deficiency	No	Steroids(CR) IVIG(CR) Rituximab(CR) Eltrombopag(CR) Romiplostim(CR) Azathioprine(NR)	6	Eltrombopag	CR	Ongoing	2	No

Figure 1: Evolution of platelet count in patients after Daratumumab.



Conclusion

Daratumumab shows clinical benefit for the treatment of immune thrombocytopenia in the heavily pretreated Immune thrombocytopenia patients. Our data demonstrate response rate of 75%. The onset of response was rapid (median of 2 weeks). Response was not durable in 2 out of the 3 patients who responded. One patient continues to be in remission after 68 weeks of follow up.

Recommendation

Larger studies are needed to confirm the benefit of of daratumumab in immune thrombocytopenia. Additionally, more research is needed on the optimal daratumumab dosing, frequency and the role of daratumumab maintenance in responders.

Acknowledgement

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