

# CLL: Common Leukemia; Uncommon Presentations

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**Abstract** We report here a series of ten patients with uncommon presentations and associations of chronic lymphocytic leukemia (CLL) not reported hitherto or occasionally reported in literature. The first two cases describe unusual causes of abdominal distension in CLL and unusual sites infiltration by CLL. The next two cases illustrate occurrence of CLL in association with other hematological malignancies. Cases five and six describe unusual infections and their impact on CLL. Cases seven and eight depict associations of rare non-hematological autoimmune conditions with CLL. The last two cases describe transformation at unusual sites. This series of ten cases illustrates how a common leukemia like CLL can present in different forms and how despite so much progress in

understanding of this leukemia so little is known of such presentations.

**Keywords** Chronic lymphocytic leukemia · Rare presentation · Infiltration · Infection · Autoimmunity · Transformation

## Introduction

Chronic lymphocytic leukemia (CLL) is the commonest leukemia in the west with CLL accounting for nearly 30 % of all adult leukemias. A study from this center had shown that CLL accounted for only 13.56 % of all adult hematological malignancies [1]. We report here a series of ten patients (groups of two each) with uncommon presentations and associations of CLL.

## CLL at Unusual Sites

When a case of CLL presents with abdominal distension and pedal edema, it is commonly due to splenomegaly or abdominal lymphadenopathy. The following two cases highlight the fact the CLL presentation may not follow textbook descriptions.

## Case 1

A 68 year old lady known RAI 0 CLL (absolute lymphocyte count  $48.37 \times 10^9/L$  at baseline), Zap70 and CD38 negative, on observation progressed over 2 years. She presented with fatigue, abdominal distension and pedal edema. On clinical examination she had pallor, cervical lymphadenopathy  $2 \times 2$  cm and ascites. Investigations revealed hemoglobin of 84 g/L, platelet count of  $64 \times 10^9/L$

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and absolute lymphocyte count of  $255 \times 10^9/L$ . She had massive ascites with spleen of 15 cm on ultrasound. Ascitic fluid analysis revealed a total of 700 cells (80 % lymphocytes), protein of 0.3 gm %, serum ascites albumin gradient of 1.8, adenosine deaminase (ADA) 13 U/L, amylase 63 mg/dL, cholesterol 25 mg/dl, triglycerides 63 mg/dL. Flow cytometry of the ascitic fluid confirmed the CLL immuno-phenotype of the lymphocytes (Fig. 1). She is currently being treated with standard dose CVP.

#### Case 2

A 50 year old lady known RAI 0 CLL (absolute lymphocyte count  $25.5 \times 10^9/L$  at baseline), Zap70 negative and CD38 positive, on clinical observation presented 2 years later with a history of abdominal distension and pedal edema. Investigations revealed she had mild ascites, bilateral renal enlargement, with a mass at the upper pole of right kidney. Her ALC at this time was  $197.2 \times 10^9/L$ ; hemoglobin was 90 g/L and proteinuria (8.7 gm/24 h), serum albumin 2.6 mg/dL, total cholesterol 405 mg/dL. A renal biopsy to investigate for the cause of nephrotic syndrome showed membranoproliferative glomerulonephritis (MPGN) (Fig. 2), while the fine needle aspirate from the renal mass at the upper pole of right kidney revealed infiltration by CLL. Considering the possibility of the paraneoplastic manifestation of nephrotic syndrome associated with CLL, she was treated with four cycles of bendamustine (100 mg/m<sup>2</sup>) and rituximab (375 mg/m<sup>2</sup>). Following this the proteinuria resolved (0.26 gm/24 h), the renal mass regressed. She is asymptomatic for the past 1 year and continues to be in complete remission.

Review of literature showed few isolated cases reporting these unusual presentations. In a case of CLL presenting with abdominal distension and pedal edema the following differential diagnosis should be considered.

1. Abdominal lymphadenopathy and splenomegaly (Most common).
2. *Nephrotic syndrome* [2] Although various case reports have shown that any glomerular pathology can accompany CLL, most common is membranoproliferative glomerulonephritis [3]. Few have proposed this to be a paraneoplastic manifestation of CLL [4].
3. *Ascites* various causes of ascites in CLL have been proposed. Chylous ascites may be due to lymphatic obstruction, Transudative ascites may be due to hepatosplenomegaly and portal hypertension, hepatic venous obstruction. Lastly infiltration of the peritoneum may be an explanation for malignant ascites.
  1. Chylous [5].
  2. Malignant [6–10].
  3. Transudate [10, 11].

4. *Gastrointestinal infiltration* [12, 13] CLL infiltration has been described in all parts of the GI tract from the stomach to the colon, however the clinical presentation is as an occult or evident GI bleed and rarely as a mass in the abdomen.

#### CLL as a Surprise

Though CLL is known to be associated with a higher risk for secondary malignancies, most of these are solid cancers [14] and therapy related myeloid neoplasms are seen in reference to the chemotherapy given for treatment of CLL [15]. The following two cases are interesting as to what the pathogenesis might be for the development of a clonal lymphoid disorder in a known case of clonal myeloid and plasma cell disorder.

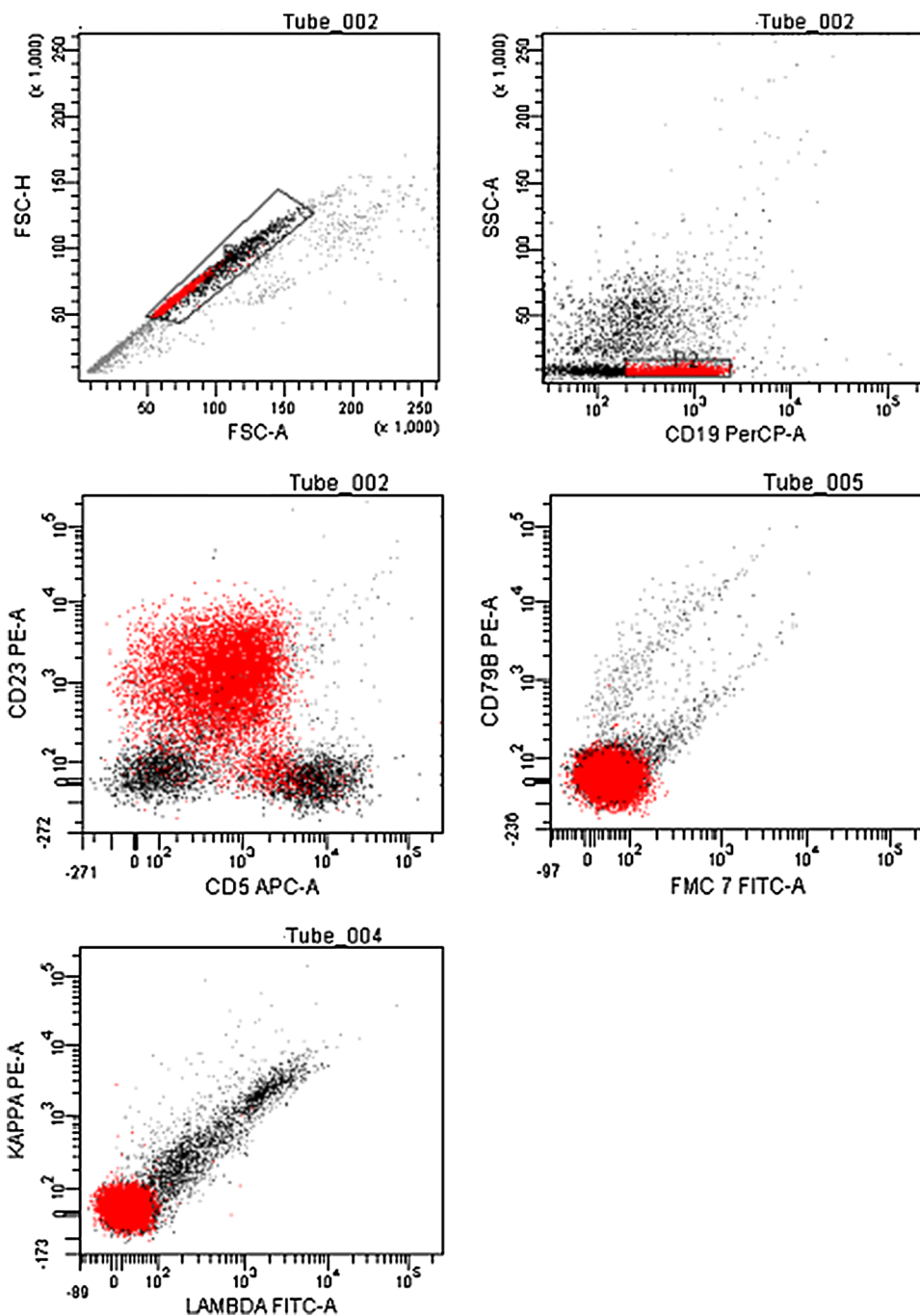
#### Case 3

A 45 year old lady diagnosed accelerated phase chronic myeloid leukemia in 2011, on imatinib 600 mg initially, hiked to 800 mg/day for failure to achieve complete hematologic response. A year and a half later she presents with cervical lymphadenopathy, anemia (Hb 82 g/L), absolute lymphocyte count  $36.9 \times 10^9/L$  and thrombocytopenia (platelet  $35 \times 10^9/L$ ). A bone marrow at this time point showed flow cytometry consistent with CLL. Zap70 was negative and CD38 was positive. Bone marrow cytogenetics showed CML was in complete cytogenetic response (0/30) and Rq-PCR for Bcr-Abl was major molecular response (0.95 %). In view of severe cytopenias the imatinib dose was reduced to 400 mg/day. She was also started on oral prednisolone at a dose of 1 mg/kg considering the possibility of autoimmune cytopenias associated with CLL. Prednisolone was tapered to 5 mg over 6 weeks and stopped after 6 months. This case was reported by the authors at this time point [16]. The last Rq-PCR for Bcr-Abl is below detection limits (IS). She is currently symptomatic with fatigue and lymphocyte doubling time less than 6 months (Hb = 91 g/L, platelet =  $68 \times 10^3/L$ , ALC =  $84.1 \times 10^9/L$ ). She is planned for treatment with bendamustine and rituximab.

#### Case 4

A 45 year old lady diagnosed plasma cell myeloma in July 2012 (BM: 70 % plasma cells), ISS stage III (b2 m = 5.95 mg/L, albumin = 3.38 mg/dL), Immunofixation IgM/kappa (M = 4.03), with related organ or tissue impairment in the form of anemia and skeletal lytic lesions. She was treated with 12 cycles of lenalidomide (15 mg) and dexamethasone (20 mg/week) and monthly

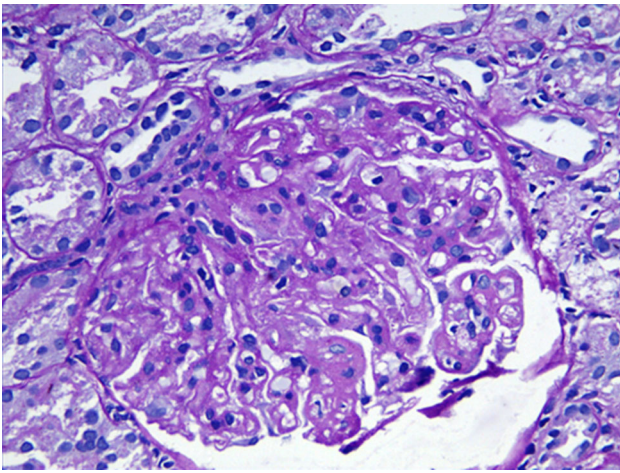
**Fig. 1** Flow cytometry of the ascitic fluid revealed lymphocyte immunophenotype corresponding to the CLL cells



ibandronate. She achieved a VGPR ( $M = 0.79$ ), however was not transplanted due to financial limitations. At the end of 12 cycles of therapy she started developing lymphocytosis ( $ALC = 16.35 \times 10^9/L$ ), BM and flow confirmed the diagnosis of CLL. Zap70 and CD38 were negative. She continues to be in VGPR from myeloma point of view, however she has pure red cell aplasia ( $Hb = 63 \text{ g/L}$ ), immune thrombocytopenia (platelet =  $80 \times 10^9/L$ ) and rapid lymphocyte doubling time

(–3 months). She is planned for lenalidomide and rituximab based therapy.

There are isolated cases reporting the occurrence of concurrent lymphoproliferative and myeloproliferative malignancies. Most of these reports had CLL preceding CML, few occurring simultaneously, but only three cases where CLL followed CML [17–19]. Cytogenetic studies have shown that the CLL was derived from the Ph negative clone [18].



**Fig. 2** Membranoproliferative glomerulonephritis in a case of CLL

Similarly there have been isolated case reports of concurrent CLL and multiple myeloma. Some studies have suggested separate clonal origin based on different cytogenetics [20], light chain restriction and IgHV rearrangement [21, 22], while some studies have shown same clonal origin based on common idiotypes and IgHV rearrangement to both these malignancies [23, 24]. Unfortunately we did not have cytogenetic profiles and IgHV status in both our cases and hence were not able to demonstrate the clonal origin to infer whether the concurrence of these cases was either coincidental or related.

#### With Unusual Infections

Patients with CLL are predisposed to a wide spectrum of infections due to inherent defects in cellular and humoral immunity and therapy related immunosuppression [25].

#### Case 5

A 60 year old gentleman presented with 6 × 8 cm, painless, ulcero-nodular midline chest swelling, left eye proptosis, external ophthalmoplegia and left parotid swelling for 3 months. On examination he had cervical and inguinal lymphadenopathy. Peripheral blood revealed lymphocytosis (ALC =  $81.2 \times 10^9/L$ ), flow cytometry of the bone marrow confirmed CLL, Zap70 and CD38 were negative. CECT imaging showed a soft tissue mass in the left orbit eroding the medial wall with extension to the lateral wall of nasal cavity and a chest wall mass eroding the sternum (Fig. 3a). While the biopsy from the nasal aspect of the orbital mass and fine needle aspiration of the parotid swelling showed infiltration by CLL (Fig. 3b, c), the biopsy from the sternal mass showed histoplasmosis (Fig. 3d). He also had pan-hypogammaglobulinemia. For cutaneous histoplasmosis he was treated with oral itraconazole 200 mg bid for 3 months

followed by once a day for 3 more months. His sternal mass healed leaving behind a scar. In view of vision threatening involvement (left eye light perception only) by CLL infiltration of the orbit he was initially treated with chlorambucil ( $45 \text{ mg/m}^2$ ) for three cycles. As there was no response he was treated with six cycles of CVP. He had recurrent chest infections during this period requiring treatment interruptions. His left eye proptosis has resolved and his vision restored (6/12). He is asymptomatic currently and continues to be on observation for CLL.

#### Case 6

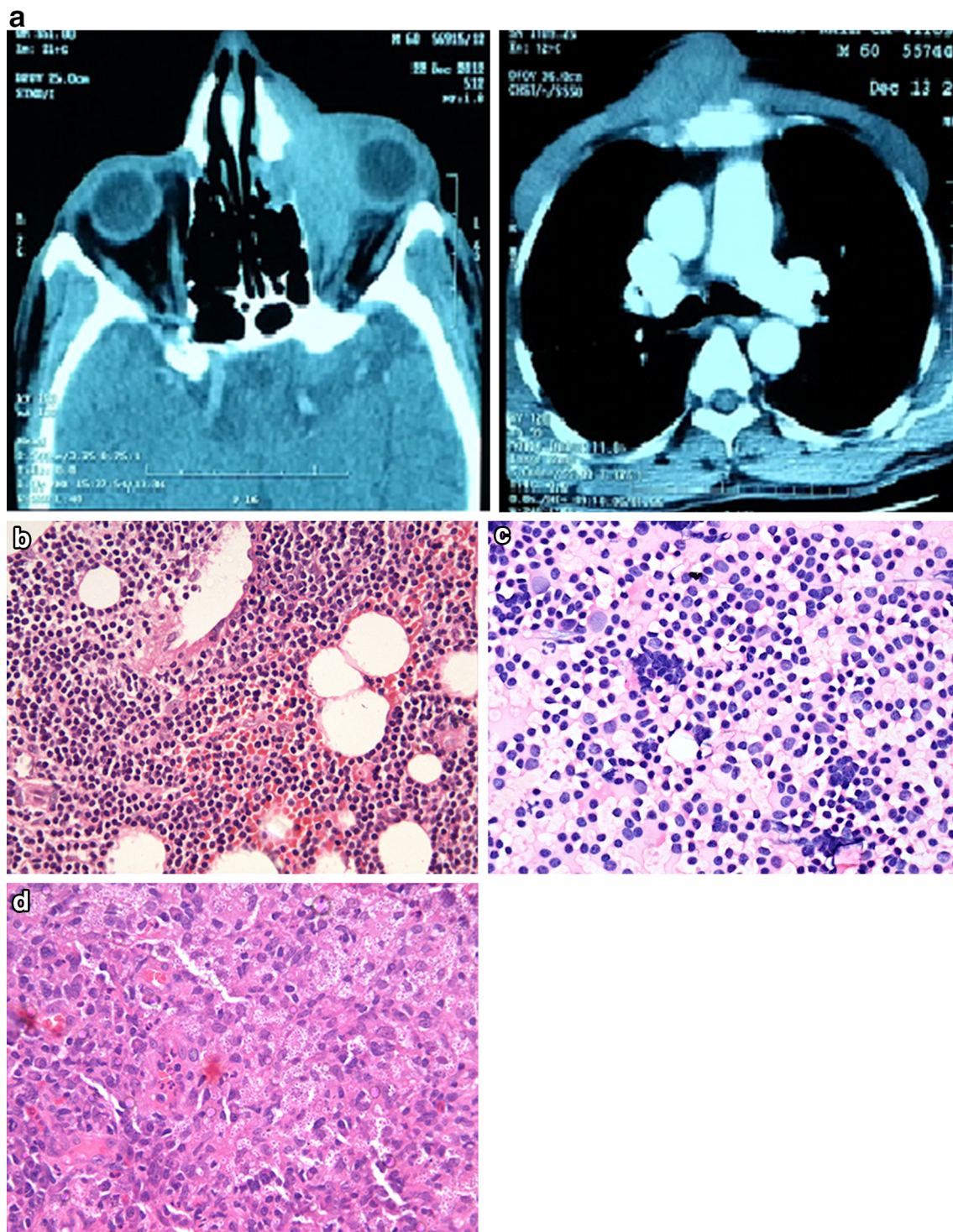
A 63 year old lady at the time of presentation in 2011 with community acquired pneumonia was found to have peripheral blood lymphocytosis (ALC =  $113.9 \times 10^9/L$ ). She also had anemia (Hb = 95 gm/L). Bone marrow and flow confirmed the diagnosis of CLL with PRCA. Zap70 and CD38 were negative. She was started on steroids 0.5 mg/kg for PRCA during which she had a partial response with Hb rising to above 100 g/L. However 3 months later she developed pulmonary tuberculosis (Brochoalveolar lavage AFB positive). She was given 6 months of anti-tuberculous therapy. During the time she was on ATT her ALC decreased progressively to  $2.5 \times 10^9/L$ , hemoglobin increased to 121 g/L. She is asymptomatic currently and continues to be on regular follow-up.

There are at least 12 case reports of the occurrence of disseminated histoplasmosis in CLL patients, however only one case reporting cutaneous histoplasmosis in CLL [26]. Though orbital infiltration by CLL has been reported previously [27–29], this case is the first report of CLL infiltrating the parotid gland. The second case is interesting in the fact that though there are case series documenting spontaneous remissions (SR) in CLL [30–33], this is the first report where SR has been seen after treatment for tuberculosis. This patient was not on any other concomitant anti-hypertensive [30] or complementary and alternative medications [34] which have been known to induce remissions in CLL. Immunological causes have been proposed for SR seen after vaccinations, viral or bacterial infections, where activation of the host cellular and humoral immune responses leading to release of cytokines, tumor necrosis factor, interferon may lead to CLL cells apoptosis and regression [35]. It would be difficult to prove whether anti-tuberculous therapy or tuberculosis itself caused CLL regression in this case.

#### Non-hematological Autoimmune Condition

#### Case 7

A 50 year old gentleman, reformed smoker (Smoking Index = 200) presented in 2005 with a history of



**Fig. 3** **a** CT showing orbital mass and chest mass eroding the sternum, **b** orbital infiltration by CLL, **c** parotid FNAC showing infiltration by CLL, **d** histopathology of the sternal mass showing histoplasmosis

intermittent claudication. During evaluation he was found to have absent right brachial, radial, femoral and bilateral popliteal, dorsalis pedis and posterior tibial pulsations. He also had a right subclavian and bilateral renal artery bruit. CT-angiography confirmed the stenosis of bilateral

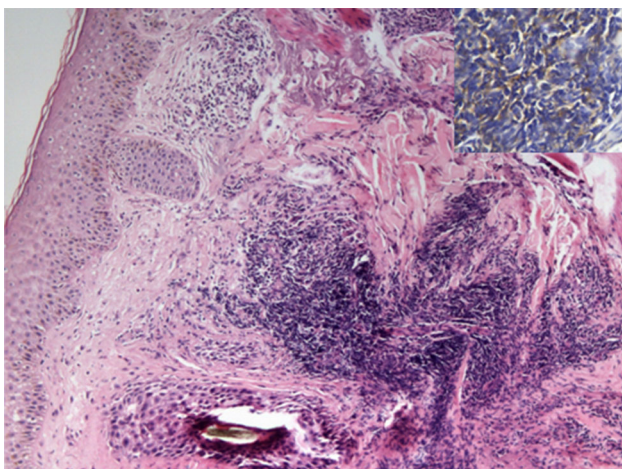
subclavian, renal artery and right common iliac artery stenosis. Considering the diagnosis of Takayasu arteritis he was managed with antihypertensives and antiplatelets. However he was lost to follow-up for the next 8 years and presented again in 2013 with intermittent claudication for

which internal iliac artery stenting was done. At this time he was incidentally found to have lymphocytosis ( $ALC = 33.7 \times 10^9/L$ ), without any lymphadenopathy or splenomegaly. Flow cytometry confirmed the diagnosis of CLL. He had improvement in his claudication symptoms post stenting of the common iliac artery; however had renal dysfunction (creatinine 2 mg/dL) related to bilateral renal artery stenosis. He remains asymptomatic and on observation from CLL point of view (Rai 0).

#### Case 8

A 60 year old gentleman had presented in 2006 with bullous skin lesions. Direct immuno-fluorescence of the skin biopsy was negative for deposition of IgA, IgG, IgM and C3. His ALC at this time was  $4.5 \times 10^9/L$ . He was managed as a case of paraneoplastic pemphigus with steroids and dapsone following which his skin lesions resolved. Six years later he presented with a papular skin eruption, lymphocytosis ( $ALC = 17 \times 10^9/L$ ) and hepatosplenomegaly. Flow cytometry confirmed the diagnosis of CLL (Rai II). Prognostic marker CD38 was positive and Zap70 was negative. Skin biopsy this time revealed perivascular and periadnexal lymphomononuclear infiltrate which was CD5+ suggesting infiltration by CLL (Fig. 4). This skin eruption also responded to oral steroids. It waxes and wanes as steroids are stopped and re-introduced. Currently his ALC is  $59.6 \times 10^9/L$ , is asymptomatic and on observation for CLL.

Non-hematological autoimmune complications are very rare in CLL. Of these paraneoplastic pemphigus and glomerulonephritis are known to be associated with CLL [36]. Vasculitis has not been described commonly with CLL. There are few case reports showing the co-occurrence of



**Fig. 4** Cutaneous (perivascular and periadnexal) infiltration by CLL cells

CLL with giant cell arteritis [37], Polyarteritis nodosa [38] and leukocytoclastic vasculitis [39]. Case seven is the first report to the best of our knowledge of the occurrence of CLL in a case of Takayasu arteritis. These autoimmune conditions are known to precede the development of CLL [40]. Cutaneous infiltration by CLL is caused by perivascular and periadnexal infiltration by CLL cells [41] as seen in case eight. It can be differentiated from cutaneous lymphocytic vasculitis; a paraneoplastic condition caused due perivascular infiltration by non-malignant T-cells [42]. This case is unique in the way that paraneoplastic pemphigus preceded CLL and the presentation of CLL was with cutaneous infiltration by malignant B-cells rather than paraneoplastic vasculitis.

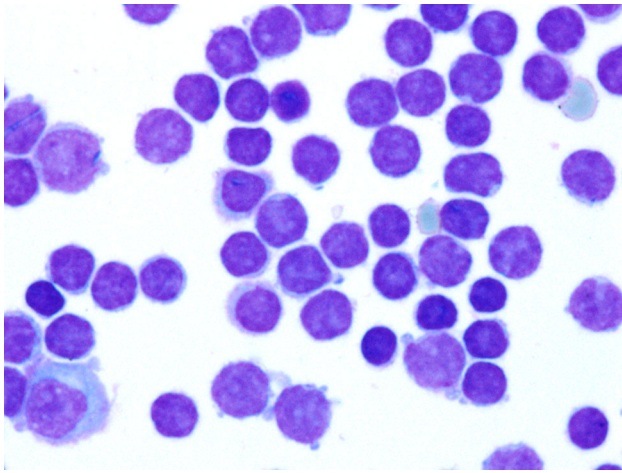
#### Synchronous DLBCL or Richter's Transformation

#### Case 9

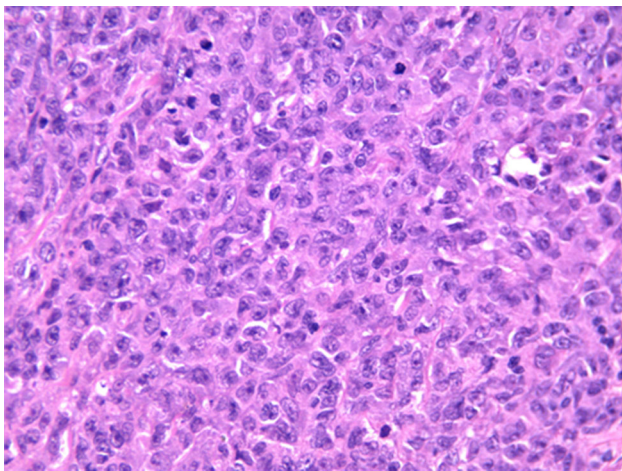
This 55 year old gentleman incidentally diagnosed CLL in 2012 ( $ALC = 17.6 \times 10^9/L$ ,  $Hb = 120\text{gm/L}$ ,  $\text{platelet} = 218 \times 10^9/L$ ). Prognostic marker CD38 was positive, Zap70 was negative. Cytogenetics showed 13q14 deletion. He presented 6 months later with holocranial headache, sudden onset vision loss and altered sensorium. He had accelerated hypertension ( $BP = 190/130\text{ mmHg}$ ). MRI brain showed lacunar infarct in left thalamus. CSF showed 20 polymorphs with normal sugar and proteins. He was treated for hypertensive encephalopathy and recovered sensorium and normal vision. Since he was asymptomatic, he was kept on observation for CLL. 3 months later he again presented with similar history of headache, giddiness and transient visual obscurations. He was normotensive this time. He had bilateral papilledema. A repeat MRI brain showed lacunar infarcts and bulky optic nerves. CSF showed 3,200 cells, all lymphocytes, proteins 140 mg/dL, sugars 45 mg/dL, ADA = 6 U. CSF malignant cytology showed infiltration by DLBCL (Fig. 5). He was treated with R-DHAP protocol.

#### Case 10

A 65 year old gentleman had presented in the year 2012 with left sided tonsillar enlargement and dysphagia. Hemogram revealed lymphocytosis ( $ALC = 29.78 \times 10^9/L$ ),  $Hb = 119\text{ g/L}$ ,  $\text{platelet} = 1.39 \times 10^9/L$ . Bone marrow flow cytometry confirmed the diagnosis of CLL, ZAP70 and CD38 was negative. He had no lymphadenopathy or hepato-splenomegaly. He was observed initially as he had no other symptoms related to CLL. However as the tonsillar swelling increased crossing over to the midline over the next 4 months, a tonsillectomy was done. Histopathological examination of the tonsillar mass revealed



**Fig. 5** CSF cytopsin smears showing infiltration by large lymphoid cells. Flow was consistent with mature B-cell lymphoma



**Fig. 6** Tonsil histopathology shows diffuse large B-cell lymphoma in a case of CLL

diffuse large B cell lymphoma (DLBCL) (Fig. 6). He was treated with six cycles of R-CHOP-21 following which he achieved a CR ( $ALC = 2.34 \times 10^9/L$ ). He was offered maintenance rituximab every 3 months. However he relapsed within 6 months ( $ALC = 21.4 \times 10^9/L$ ). Currently he has rapid lymph-node and lymphocyte doubling time. Cervical LN biopsy was suggestive of CLL/SLL and did not show high grade morphology. He is planned for therapy with BR.

Though CNS involvement by CLL is rare with less than 100 cases reported ante mortem, Richter's transformation of the CNS is even rarer with only about 17 cases reported in literature [43]. CNS Richter's can involve the brain parenchyma, leptomeninges as seen in our case or the dura mater. Optic nerve infiltration associated with leukemia meningitis has also been described in CLL [44]. Diagnosis can be

confirmed by CSF immunophenotyping as was done in our case. Treatment may include radiotherapy or intrathecal chemotherapy with or without systemic chemo-immunotherapy. There is a report of sustained response with intrathecal liposomal cytarabine [45]. Whether case ten represents Richter's transformation of CLL in the tonsils or concurrent DLBCL and CLL remains a matter of debate. There are no cases in literature reporting either occurrence to the best of our knowledge.

**Conflict of interest** All the authors declare that they have no competing interests.

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