**TITLE PAGE – LETTER TO THE EDITOR**

**Title:** Rare Skin Manifestations Successfully Treated with Primary B-cell Chronic Lymphocytic Leukemia (B-CLL) Treatment

**Running Title:** Rare skin manifestations in B-cell Chronic Lymphocytic Leukaemia

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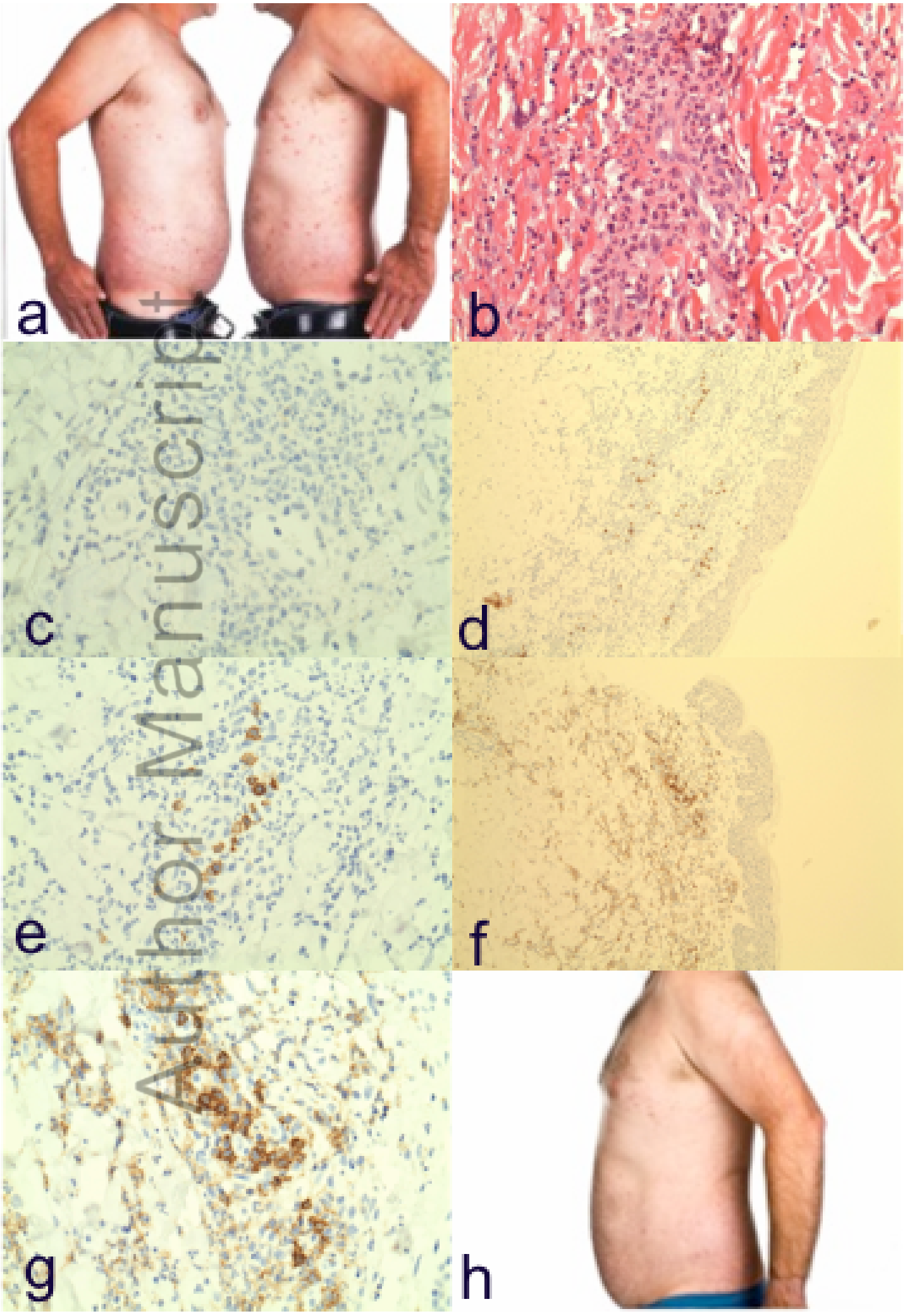
**Manuscript Word Count:** 961

**Manuscript Figure Count:** 2

**Number of References:** 6

**Keywords**

Leukemia, lymphocytic, B-cell, pyoderma gangrenosum, vasculitis



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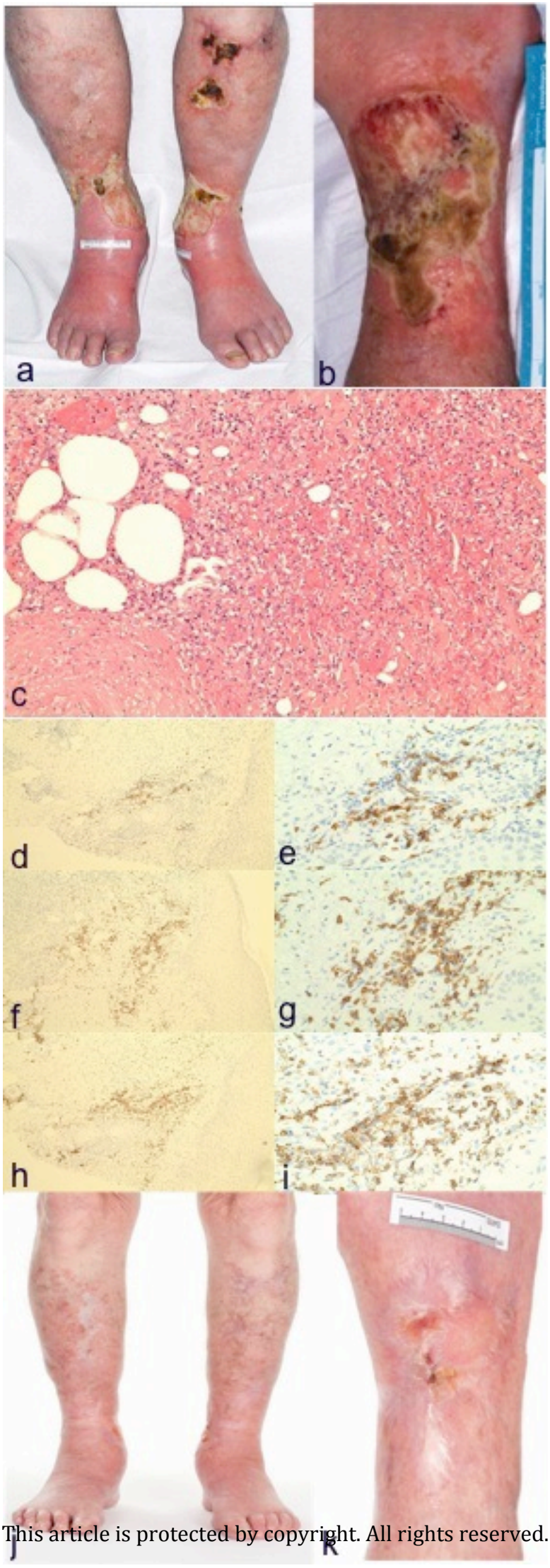

To the Editor,

B-cell chronic lymphocytic leukemia (B-CLL) is the most common leukemia in adults in Western countries with an incidence of 3-5 per 100 000 [1]. Skin manifestations in B-CLL occur in approximately 25% of patients, which are commonly skin cancers, viral infections and leukemic infiltrates [1]. We describe 2 rare skin conditions not previously reported to be associated with underlying B-CLL, in which specific anti-leukemia treatment successfully eradicated the skin lesions.

Our first case is a 69-year-old patient presenting with recurrent ulcerated lesions in his lower limbs in 2005 (Figures 1a-b). A biopsy was consistent with pyoderma gangrenosum (PG) (Figure 1c). There was a minimal B-cell infiltrate and expected T-cell distribution within an inflammatory skin infiltrate on immunohistochemistry (Figures 1d-i). His PG proved difficult to manage with multiple immunosuppressive agents including systemic and topical steroids, cyclosporine, mycophenolate mofetil and hyperbaric oxygen. His clinical course was complicated by significant pain requiring high doses of opioids, gabapentin and sodium valproate and multiple cellulitic infections requiring prolonged courses of antibiotics. In 2007, he was noted to have a lymphocytosis of $9.3x10^9$/L with normal haemoglobin, platelet count and B2-microglobulin. Peripheral blood (PB) flow cytometry confirmed an abnormal B-cell population expressing CD19+/5+/10-/20+ (dim)/22+/23+/FMC7- and surface light chain negative consistent with B-CLL. There was minimal lymphadenopathy of 12mm in the left carotid space on CT staging. A bone marrow (BM) biopsy showed 40% interstitial and nodular lymphoid infiltrate. Cytogenetics confirmed deletion of 13q and loss of Y chromosome. As he continued to remain asymptomatic from his B-CLL, there were no indications to commence systemic chemotherapy.

However, as his refractory PG showed no improvement despite the addition of monthly intravenous immunoglobulins (IVIg), he was commenced on multi-agent chemotherapy in

September 2012 with Fludarabine, Rituximab and Cyclophosphamide (FCR) for his B-CLL. He received four cycles of treatment with his last cycle complicated by sepsis, acute renal failure and BK cystitis. A restaging BM done confirmed a complete morphological remission with minimal residual disease (MRD) by flow cytometry. 16 months post-completion of treatment, his leg ulcers are almost completely resolved without the need for further immunosuppressants nor analgesics (Figures 1j-k).

Our second case is a 46-year-old patient presenting in 2008 with generalised painful and itchy urticarial lesions triggered by cold (Figure 2a). A skin biopsy showed leukocytoclastic vasculitis (Figure 2b). C3 and C4 levels were low at 0.26 g/L (0.82-1.85) and 0.12 g/L (0.15-0.53) respectively with significantly depressed activity of the classical pathway at 66% (>85%) consistent with a diagnosis of hypocomplementemic urticarial vasculitis syndrome (HUVS). Autoimmune antibody screen was negative, total cryoglobulin and IgA levels were normal.

In 2011, he was noted to have mild lymphocytosis of $4.5x10^9$/L with normal hemoglobin, platelet count, LDH and B2-microglobulin. An IgG kappa paraprotein of 5g/L was detected. Peripheral blood flow cytometry demonstrated a monoclonal B-cell population expressing CD19+/5+/10-/23+ (normal to bright)/20+/22+/79b-/FMC7- and surface lambda light chain restriction (weakly expressed) consistent with a B-CLL phenotype. A CT scan showed right axillary and inguinal lymphadenopathy measuring 3.2 cm and 1.9 cm respectively. A BM biopsy showed a small lymphoid infiltrate of 5-10% and cytogenetics showed deletion of 13q. Further immunohistochemistry showed very rare CD20+ cells and a normal T-cell distribution in his skin biopsy (Figure 2c-g). There were no indications for treatment of his Stage A B-CLL.

However, his HUVS was difficult to manage with antihistamines and multiple immunosuppressive agents including steroids, hydroxychloroquine, azathioprine and methotrexate. He was then treated with two doses of Rituximab 500mg/$m^2$ in September

2013. This resulted in normalisation of his lymphocyte count within days and an almost complete resolution of his skin lesions by 4 months sustained off any immunosuppressive therapy (Figure 2h).

Pyoderma gangrenosum (PG) is a rare disorder with more than half the patients having an underlying systemic disease, predominantly inflammatory bowel disease, seronegative arthritides and myeloid hematological malignancies [2] with no reported occurrence in B-CLL [2]. Successful treatment of the underlying disease can result in improvement of PG. The initiation of systemic chemotherapy for patient GK was not due to progressive B-CLL but primarily for management of his refractory PG, which successfully resolved his skin ulcers without the need for further immunosuppression.

Urticarial vasculitis (UV) is an uncommon disorder which has a prevalence of <5% in patients with chronic urticaria [3]. It can occur in association with autoimmune disorders, infections, drug reactions or rarely, solid organ malignancies with no reported cases in B-CLL. However, paraneoplastic lymphocytic vasculitis has a reported incidence of 9.5% in patients with underlying lymphoproliferative disorders (B-cell NHL and CLL) occurring after a median duration of 18 months [4]. Responses in the primary hematological disorder and skin disease to multiagent chemotherapy are variable with discordance in the time course of responses.

Rituximab as a single agent has been useful in the management of refractory UV by targeting mature and malignant B-lymphocytes expressing the CD20 cell-surface marker [5]. The immune dysregulation in HUVS is thought to be driven by immune complex deposition in the dermal blood vessels from B-cell hyperreactivity. Rituximab has been used successfully to treat refractory autoimmune systemic disorders and autoimmune hemolytic anemia and/or thrombocytopenia. Its use in idiopathic PG has not been reported and paradoxically, rituximab has been implicated as the cause of vulvovaginal PG [6].

These 2 cases illustrate previously unreported rare skin conditions *predating* the diagnosis of B-CLL, in which definitive treatment of the primary hematological condition resulted in resolution of these skin manifestations refractory to multiple immunosuppressive treatments. These improvements are postulated to be likely due to an indirect effect of the rituximab and/or multiagent chemotherapy on the immune dysregulation arising from the malignant B-cell clones rather than a direct therapeutic effect on the skin lesions since in both of our cases, there was a lack of significant B-cell infiltrates in the skin biopsies prior to commencing B-CLL treatment.

**Conflicts of Interests**

S.W, J.McC, J.D, A.T and L.C: Nothing to disclose

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