Comment on: type 1 cryoglobulinaemia leading to gangrene of the toes and ischaemic ulceration

Thanks to Siow et al (2018) for sharing their experience of diagnosing and managing type 1 cryoglobulinaemia.

I just wish to clarify what radiological imaging was undertaken, given that type 1 cryoglobulinaemia results from monoclonal expansion of B cells?

Whilst it is stated the patient ‘did not fulfil the diagnostic criteria for multiple myeloma’, presence of osteosclerotic lesions (as we have also encountered in a patient presenting with type 1 cryoglobulinaemia and a normal bone marrow aspirate), or, one supposes, a solitary plasmacytoma or indeed any lymphadenopathy, would change the patient’s management.

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I read with great interest the recent article by Siow et al (2018) regarding type 1 cryoglobulinaemia leading to gangrene of the toes and ischaemic ulceration. I would like to add some points.

Type 1 cryoglobulinaemia is usually asymptomatic, but when symptomatic it is associated with findings of hyper viscosity and vascular occlusions due to immunoglobulins, which precipitate in the generally colder body regions. Raynaud phenomenon, livedo reticularis and digital ischemia can develop. Usually, type 1 cryoglobulinaemia is associated with multiple myeloma, Waldenström macroglobulinaemia, chronic lymphocytic leukaemia and monoclonal gammapathy of unknown significance (den Hollander & Swaak, 2002).

Sometimes the first finding of underlying disease may be type 1 cryoglobulinaemia-related symptoms and findings. Therefore, the patient’s primary disease will be missed and the diagnosis will be delayed because there are no additional symptoms or findings associated with the underlying disease. If type 1 cryoglobulinaemia is not included in the preliminary diagnosis and not investigated as recommended (Ferri et al, 2002), it can easily be overlooked. At this point, these patients are followed up for incorrect diagnoses, such as connective tissue diseases, vasculitis and Buerger disease, with delays in effective treatments and increased morbidity. For this reason, dermatologists, rheumatologists, haematologists and cardiovascular surgeons should be alert for similar cases and made aware of the significance of this disorder.

I hope that the above-mentioned items might add to the value of the well-written article by Siow et al (2018).
A retrospective multicentre study of COCKLE, an oral chemotherapy regimen, as palliative treatment for high grade lymphoma

There is no standard of care for the treatment of relapsed high-grade lymphoma, in patients not fit for salvage chemotherapy and those who relapse following autologous stem cell transplantation. The prognosis for these patients is poor, and minimising treatment burden and side effects should be prioritised in treatment decisions. Several oral chemotherapy regimens are used in different centres, with the aim of prolonging survival and treating disease-related symptoms while minimising toxicity. In Bristol, UK, an oral regimen called COCKLE, named after the first patient treated, has been in use since 1995. This regimen has also been used as first line treatment in very elderly or frail patients, who are not fit for R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone) or other curative-intent regimens. It consists of flat doses of lomustine 80 mg day 1, cyclophosphamide 100 mg days 1–10, etoposide 50 mg days 1–10 and prednisolone 60 mg days 1–7. Latterly, rituximab has been added for those with CD20-positive disease. We report a retrospective observational study of this regimen, from two centres in Bristol, in patients treated between 2012 and 2017.

Seventy-one patient records were identified from cancer databases and screened; of these patients, three never received treatment, notes were not retrievable in two and one had low-grade lymphoma. We report on the 65 cases of adults with high grade lymphoma who received at least one dose of COCKLE. Patient characteristics are detailed in Table SI. The median age in the relapsed cohort was 75 years, which is consistent with other studies, and 84 years in those treated first-line. The majority of patients had diffuse large B-cell lymphoma (DLBCL), with Hodgkin lymphoma (HL) the next most common at 18% of the relapsed cohort. Both cohorts had multiple predictors of poor outcome: overall, 86% were stage 3–4, 78% had an international prognostic index (IPI) of 3–5 and 42% were performance status 3–4. Among the relapsed cohort, 16 (47%) had received ≥2 prior lines of therapy.

The median number of cycles of COCKLE received was 3 in the first-line cohort, and 2–5 in the relapsed cohort; 24 patients (37%) had prospective dose reductions due to comorbidity or poor performance status. 18 patients (28%) received at least one dose of rituximab. Overall, 31 patients (48%) obtained a partial or complete response, determined either radiologically or by clinical examination where peripheral disease was palpable. There were more complete responses in the first-line cohort (7 vs. 4). Toxicity was significant, with 30 patients (46%) requiring admission for grade 3–4 infection during treatment, and 26 (40%) developing grade 3–4 neutropenia. The mean number of days spent as an inpatient during treatment was 12.

As would be expected, overall survival (OS) was significantly longer in the first-line group (median 275 vs. 148 days, P = 0.02), and it was longer in those attaining at least a partial response (median 314 vs. 95 days, P < 0.0001) (Fig 1). Three patients in the first-line cohort (10%) remain alive and progression-free beyond 24 months, 2 of whom also received consolidative radiotherapy. The median OS of 8.3 months is comparable with other studies of palliative treatment in high-grade lymphoma. A French series reported median OS of 1.2 years, but that cohort had better performance status and lower IPI, and 47% received anthracycline regimens (Thieblemont et al, 2008). Since COCKLE was devised, there has been considerable data on the use of dose-reduced RCHOP in the frail population. A prospective phase II study of mini-CHOP reported a median OS 29 months in patients aged >80 years (Peyrade et al, 2011), and a