Herpes simplex virus typically presents as a self-limiting vesicular rash. However, cutaneous presentation in the immunocompromised is often atypical, posing a diagnostic challenge and results in delayed treatment. We describe two cases of atypical presentations of genital herpes simplex virus (HSV-2) in chronic lymphocytic leukemia (CLL).

CASE REPORTS

**Patient 1.** A 70-year-old Afro-Caribbean man who was seen with a 6-month history of an enlarging, weeping, painless ulcer on his glans penis. He had been diagnosed with CLL 4 years previously and not been given cytostatic or other treatment previously. He had been referred by the Hematology and Urology services at another hospital to the Regional Penis Cancer Multi-Disciplinary Team (MDT) (which includes representation from Dermatology) at our institution for exclusion of squamous cell carcinoma of the penis. Examination revealed a cellulitic, edematous penis and glans with the latter showing tumidity, vegetative change and superficial erosions (Fig. 1). There was bilateral inguinal lymphadenopathy. Several penile biopsies had already been taken from the lesion. These showed surface ulceration with a dense chronic inflammatory infiltrate in the dermis predominantly composed of plasma cells and fewer lymphocytes. Immunostaining with CD5 and CD23 showed no evidence of infiltration by CLL. Microbiological cultures showed *Staphylococcus aureus* and mixed anaerobes. Cultures for acid-fast bacilli, atypical mycobacterium and fungi were negative. HSV-2 was detected by PCR on skin swab. The penile lesion initially healed following treatment with a combination of aciclovir and ciprofloxacin, but then relapsed to remit on further treatment with famciclovir and inosine prabonex. The patient has remained lesion free on long-term prophylactic famciclovir.

**Patient 2.** A 76-year-old heterosexual Caucasian man who was initially referred by the Dermatology services at another hospital to the Urology Department at our institution with an ulcer on his penis. He had been diagnosed with CLL 18-months previously. No previous cytostatic or other treatment had been given. Excision of the penile lesion was performed. On histological examination chronic ulceration was seen with a chronic inflammatory infiltrate in the dermis. Immunohistochemistry for HSV was negative. The penile lesion did not recur. However his case was discussed at the Regional Penis Cancer MDT and his management transferred to the Dermatology Department because of concern about a potential skin neoplasm on his right buttock. He gave a 12-month history of a persistent, painful, slightly ulcerated red nodule measuring $30 \times 20$ mm in diameter. Herpetic infection was suspected clinically. HSV-2 was confirmed by PCR on the skin swab. He was treated with aciclovir 400 mg 5 times daily for 2 weeks. The skin lesion resolved and healed with post-inflammatory inflammation.

**DISCUSSION**

Chronic erosive anogenital HSV is classically associated with untreated human immunodeficiency (HIV) infection (1). Chronic erosive and verrucous HSV is rarely seen in patients with HIV treated with antiretrovirals and is an example of immune recon-
stitution inflammatory syndrome (IRIS) (2). CLL is characterized by progressive defects in humoral- and cell-mediated immunity (3) predisposing to increased risk of infection. Cell-mediated immunity to HSV is largely dependent upon the function of natural killer (NK) cells, macrophages and CD4 and CD8 lymphocytes (4). HSV antigens directly activate NK cells, which upregulate HLA-DR and HLA-DQ and activate CD4 T lymphocytes (5). It is worth nothing that HSV HIV IRIS cases have not been reported in Caucasians, raising the possibility of an immunogenetic factor in HSV pathogenesis but their exact interaction remains to be determined (3). Immunogenetic profiling was not performed in either of these cases.

HSV2 typically presents as acute, painful, self-limiting attacks of erythematous papules and vesicles in the anogenital region. However, in the immunocompromised, the presentation can be chronic and atypical: generalised papular eruption, linear erosive ulceration, nodules, herpes simplex vegetans (6) or, as in this case, a verrucous growth clinically simulating a neoplasm in patient 1. The course of presentation in patient 2 was protracted. The morphology and anatomic location of his lesion was also unusual. The advances in new cytostatic agents and monoclonal antibodies being used in CLL have created more profound immunosuppression in CLL patients. Hence, atypical HSV may be an increasing problem (7). Whilst HSV can rarely mimic a tumour in the immunosuppressed, the two conditions can co-exists (8). Diagnosis of HSV infection can usually be made by history, physical examination and confirmed by PCR in muco-cutaneous swabs as the preferred diagnostic method (9).

Aciclovir, valaciclovir and famciclovir are all effective for genital herpes infection (9). HSV resistance to aciclovir in immunocompetent patients is rare with a reported prevalence of 0.3%, compared with the immunocompromised where it varies between 4% to 7% (10–12). If aciclovir resistance is present, it is unlikely that the patient will respond to aciclovir, valaciclovir or famciclovir. In these cases, foscarnet, vidarabine, cidofovir or imiquimod can be used (13, 14). Bacteriological and virological investigations should be repeated. Aciclovir resistance testing was attempted in patient 1 on several occasions but no HSV could be isolated so testing proved impossible. Clinically, aciclovir resistance seems likely in this patient.

In conclusion, we describe two cases of herpesvirus infections in CLL, of which one presented as chronic erosive verrucous herpes simplex of the penis similar to HSV IRIS in HIV. In this case, the atypical presentation mistakenly triggered referral to a tumour specific MDT because a penile cancer was suspected. The second case presented with a protracted, atypical cutaneous plaque on the extragenital site and again cutaneous neoplasia was erroneously suspected. It is imperative to inculcate a high index of clinical suspicion to prompt early diagnosis and management.

The authors declare no conflicts of interest.

REFERENCES