Clinical Case Reports

A case of refractory chronic lymphocytic leukaemia with an unusual course

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ABSTRACT

Chronic lymphocytic leukaemia (CLL) is a heterogeneous disease with uncertain course. Treatment should be tailored to the patient's disease as well as the prognostic subgroup. With the increased use of rituximab as well as other selective and non-selective immunomodulatory agents, the incidence of infectious complications and second malignancies has also increased. Progressive multifocal leucoencephalopathy (PML) is a complication of rituximab in HIV-negative patients. A 56-year-old male with CLL had been treated and relapsed four times in 6 years. Rituximab was added to the combination after the second relapse and repeated in the third relapse in combination with bendamustine. In the seventh year of diagnosis, relapse of CLL and an ulcerated tumorous lesion was observed in the left index finger, which progressed in 3 months and was later diagnosed as angiosarcoma. The cancer was treated with local radiotherapy and combination chemotherapy. One year after the last rituximab exposure, progressive muscle weakness developed and polyoma JC virus DNA was observed with increased titres in the cerebrospinal fluid, and the patient was diagnosed as having PML. The patient died 2 months later. Our patient had an unusual course of CLL over 8 years, with relapses, complicated with a secondary malignancy and an infectious complication.

Natl Med J India 2019;32:347–9

INTRODUCTION

Chronic lymphocytic leukaemia (CLL) is a heterogeneous disease with protean manifestations and an uncertain course. There are several initial treatment options but most have not been compared directly. Patients with CLL have abnormal cellular and humoral-mediated immune responses due to the underlying disease process or to chemoimmunotherapy used for treatment. Patients with CLL/small lymphocytic lymphoma (SLL) may also have a higher risk of developing secondary solid tumours such as Kaposi sarcoma, malignant melanoma and cancers of larynx and lungs.

Progressive multifocal leucoencephalopathy (PML) is a demyelinating disease of the central nervous system (CNS) with a severe course, caused by re-activation of the polyomavirus JC (JC virus). The primary infection is usually asymptomatic in childhood and antibodies can be found in a majority of adults. First described in patients with lymphoproliferative and myeloproliferative diseases, PML occurs almost exclusively in immunosuppressed individuals, transplant recipients and with the use of certain drugs.[1] We report a patient with relapsed and refractory CLL, who developed angiosarcoma and eventually PML.

THE CASE

A 56 year-old male was diagnosed with CLL during a routine check-up programme and referred to us for evaluation. He had no complaints, had chronic hepatitis B virus infection (hepatitis B surface antigen positive, hepatitis B surface antibody negative, transaminases were normal and HBV DNA was 100 copies/ml). The presenting stage of CLL was stage I (haemoglobin 14.5 g/dl, haematocrit 48%, total leucocyte count 12 800/cmm, lymphocyte count 8400/cmm, platelets 243 000/cmm) and the treatment decision was made based on the lymphocyte doubling time of 3 months. The patient was HIV-negative. Fluorescent in situ hybridization (FISH) was negative for 17p, 13q and 11q deletions. Starting with prophylactic lamivudine treatment, after 6 cycles of fludarabine-cyclophosphamide (FC), he was in remission for 3 years. The first relapse occurred with decreased lymphocyte doubling time (2 months) and after 4 cycles of FC the patient had a remission for 2 years. The second relapse occurred with decreased lymphocyte doubling time (3 months), deletion for 17p mutation was negative and after 4 cycles of rituximab and high-dose methylprednisolone, the remission lasted for a year. The third relapse also presented with decreased lymphocyte doubling time (3 months), and repeated analysis for deletion of 17p and ZAP70 were negative. Four cycles of rituximab plus bendamustine were given and the patient remained refractory. Within 6 months, conglomerated bulky masses were observed within the mediastinum and the abdomen as well as on the neck and axillae. Lymph node biopsy revealed SLL. At the same time, an ulcerated tumorous lesion was observed on the left index finger which progressed in 3 months and was later excised and diagnosed as angiosarcoma (Figs 1 and 2). Local radiotherapy and cyclophosphamide-doxorubicin-vincristine-methylprednisolone were started.[2] After 2 cycles of treatment, the patient had progressive neurological symptoms including dysarthria, dysphagia and progressive muscle weakness. On magnetic resonance imaging, increased signal on T2-weighted images and hyperintensity on diffusion-weighted sequences were observed (Fig. 3). Cerebrospinal fluid analysis revealed polyomavirus JCV DNA (172 000 copies/ml). The patient was diagnosed as having PML, and plasmapheresis and pulse corticosteroids (1 g/day methylprednisolone) were started. However, his clinical condition deteriorated and he died 2 months after the diagnosis.

DISCUSSION

According to the WHO 2016 classification of neoplasms, CLL is regarded as identical to SLL which is a mature (peripheral) B-

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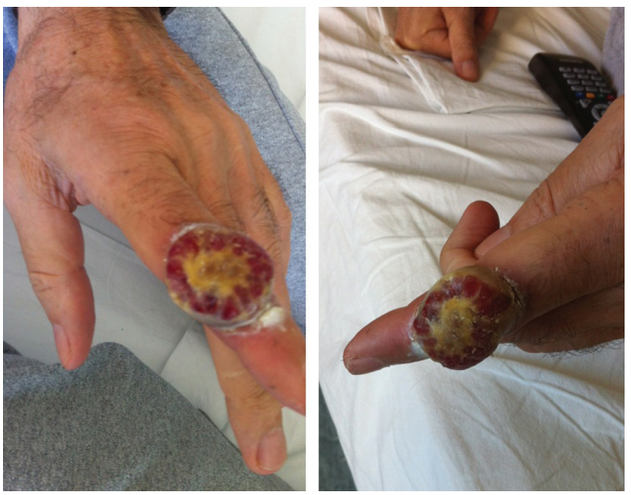

FIG 1. Ulcerated tumour on the left index finger

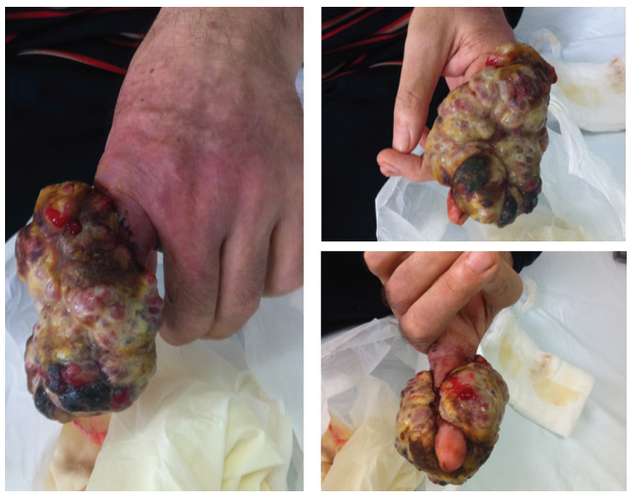

FIG 2. Progression of the tumour over 3 months

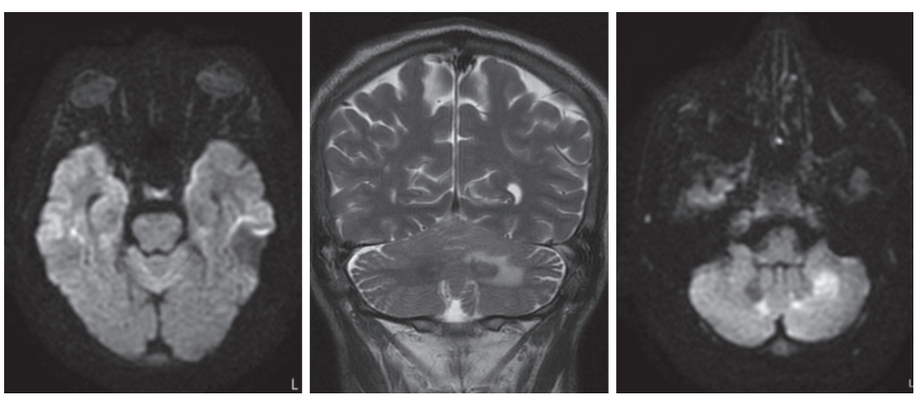

FIG 3. Magnetic resonance imaging showing increased signal on T2-weighted sequences and hyperintensity on diffusion-weighted sequences

cell neoplasm. There is a general conviction that CLL is an indolent disease with a prolonged clinical course, and mortality may be unrelated to CLL. However, this is true for only a small group of CLL patients. Survival is reported to range from 2 to 20 years (median 10 years).[3] Several prognostic factors have been proposed and evaluated to predict the course of early-stage CLL including age, sex, degree of lymphocytosis, morphological features of blood lymphocytes, the proportion of prolymphocytes chromosomal karyotype and levels of serum immunoglobulins.[4] There are several treatment options for treatment-naive patients. The available regimens differ with regard to time to progression and treatment-related toxicities, but overall survival rates are similar. The choice between these regimens should be made according to patient characteristics. The goals, intensity and duration of therapy for CLL are not clear and the evidence regarding the necessity of maintenance therapy is scarce. Most patients show an initial or partial response though eventually, relapse occurs and almost all patients with CLL will ultimately develop refractory disease. Patients with CLL have a higher risk of developing other haematological and solid malignancies. This tendency may be due to underlying disease, chronic immunosuppression and treatments for CLL. The most frequent secondary cancers include Kaposi sarcoma, melanoma, larynx and lung cancers. Patients with CLL also have abnormal immune responses due to the nature of the underlying disease and immunosuppressive treatment for infections are responsible for 50% of mortality in patients with CLL. Besides the increased rates of bacterial infections, reactivation of herpes viruses is also common.[5] Patients treated with purine analogues (e.g. fludarabine) are at increased risk of opportunistic infections. Patients treated with alkylator-based regimens (e.g. chlorambucil) have frequent infections of the respiratory tract, most commonly bacterial. Patients treated with rituximab have an increased risk of viral infections, especially hepatitis viruses.[6] PML is a demyelinating disease of the CNS with a severe course that is caused by JC virus reactivation.[7] Primary asymptomatic infection is frequent in early childhood and in the majority of adults. JC virus remains latent either in the kidneys or lymphoid organs, and with the development of cellular immunosuppression, the virus may be reactivated, reaching the CNS causing lytic infection of CNS myelin-producing cells, and oligodendrocytes. The importance of our case is that immunosuppressive treatment is based on B-cell depletion, but PML is frequently observed in cellular type immunosuppression. The intrinsic immune dysregulation CLL, treatment combinations involving corticosteroids, and cytotoxic

treatments may be the reason for PML in this patient.[8] PML occurs almost exclusively in immunosuppressed individuals. It has been reported in patients with solid organ malignancies, granulomatous and inflammatory diseases, solid organ transplant recipients, and with the use of immune suppressive drugs.[9,10]

Conclusion

Our patient was in the early stage at presentation but had several relapses of CLL though never matched the criteria of stage III or IV disease. Treated with internationally accepted agents and protocols, our patient ultimately had a refractory disease. As for complications, we observed a secondary malignancy angiosarcoma, complicating the course and also the quality of his life. Eventually, mortality came with the severe course of PML. Our patient had a challenging course of CLL with dreadful complications.

Conflicts of interest. None declared

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