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HIV-associated splenic diffuse large B-cell lymphoma combined with hepatitis C and tuberculous meningitis:A case report

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ABSTRACT

Diffuse large B-cell lymphoma (DLBCL) is a highly aggressive B-lymphocyte-derived malignant proliferative disease that is currently one of the leading causes of death in HIV patients. The incidence of lymphoma in HIV patients is 60–200 times higher than in the general population compared to the non-HIV population, and diffuse large B-cell lymphoma can cause numerous disease manifestations, especially in severely immunocompromised individuals. We treated a case of HIV-associated splenic diffuse large B-cell lymphoma combined with hepatitis C and tuberculous meningitis. In this case, diffuse large B-cell lymphoma of the spleen was difficult to diagnose. Second, simultaneous treatment of multiple diseases requires consideration of drug interactions. Our case highlights the diagnostic value of early tissue biopsy and the importance of avoiding drug interactions during treatment, and the selection of appropriate CART, anti-hepatitis C, and anti-tuberculosis protocols to reduce mortality from diffuse large B-cell lymphoma comorbidification.

1. Introduction

DLBCL remains a global health problem, particularly in under-resourced communities and populations affected by the HIV pandemic, and is a group of tumours consisting of moderately large to large B-lymphocytes with nuclei equal to or greater than the nuclei of normal macrophages or twice the size of normal lymphocyte nuclei, with a diffuse growth pattern and a gold standard pathological diagnosis. Compared to non-HIV populations, HIV patients are at significantly higher risk of developing tumours, associated with defective cellular immunity, inflammatory responses, cytokine dysregulation and oncogenic viruses due to HIV infection, and DLBCL is currently one of the leading causes of death in HIV patients in China [1]. DLBCL occurs mainly in older adults, with a median age of 60–70 years, and is slightly higher in men than in women. Approximately 40% of DLBCL has an extra-nodal origin and can be seen in any extra-nodal site, with the gastrointestinal tract being the most common and other extra-nodal sites including bone, testis, spleen, pharyngeal lymphatic ring, salivary glands, thyroid, liver, kidney and adrenal glands. We have seen a rare case of a patient with diffuse large B-cell lymphoma of the spleen, HIV infection, hepatitis C and tuberculous meningitis.

2. Clinical case

A 46-year-old male HIV-infected patient was referred from a local hospital with a history of fever, abdominal pain and weight loss 1

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month prior to admission. External blood cultures were negative and routine blood tests suggested a trilineage reduction (WBC 1.75 × 10^9/L, HGB 102 × 10^9/L, PLT 81 × 10^9/L). Bone marrow cytology suggested hypersplenism with inability to exclude, neutrophilic changes in granulocytes and mildly elevated monocyte and histiocyte ratios. An abdominal CT examination suggested an enlarged spleen with multiple occupying lesions. The patient's clinical symptoms did not resolve after antibacterial treatment was given, and a preliminary diagnosis of malignant lymphoma was possible. The patient complained of a history of intravenous injection of heroin by sharing syringes 20 years ago. 6 months ago, the patient developed fever and headache with impaired consciousness and was diagnosed with tuberculous meningitis at the local hospital and treated with anti-tuberculosis with HRE (isoniazid, rifampicin, ethambutol),the clinical symptoms were relieved Without hormone therapy,and was also diagnosed with HIV infection and positive for hepatitis C. HIV-RNA and HCV-RNA were not measured,He was not treated with antihepatitis C and received Tenofovir 300mg/day + Lamivudine 300mg/day + dotiravir 50mg/day fixed-dose combination antiretroviral therapy (CART) combination therapy.During the follow-up, there was no fever, no abnormality in blood routine and liver and kidney function.

He was admitted to hospital due to "fever and left upper abdomen pain for more than 10 days", mainly low fever in the afternoon, body temperature up to 38 °C, dull pain in the left upper abdomen, accompanied by weight loss of 3 kg.On admission: T37.5 °C, P89 beats/min, R18 beats/min, BP103/67 mmHg, height 170cm, weight 60kg, BMI 20.76kg/m^2, clear consciousness, no palpable enlargement of superficial lymph nodes, subsplenial margin palpable 5cm below the left costal margin, hard texture, smooth surface. Routine blood tests were WBC 1.72 × 10^9/L (reference range 4 ~ 10 × 10^9/L), HGB 99g/L (reference range 130 ~ 160g/L), PLT 62 × 10^9/L (reference range 100 ~ 300 × 10^9/L), normal coagulation tests, CD4 count 100 cells/uL, blood β-microglobulin 4.98mg/ AST35U/L (reference range 0 ~ 30U/L), ALT18U/L (reference range 0 ~ 20U/L), LDH493U/L (reference range 0 ~ 295U/L). (reference range 0 ~ 295U/L). CT abdomen suggested splenomegaly with multiple occupying lesions (Fig. 1), PET-CT showed large and uneven density of the spleen and S4 nodules in the liver; multiple lymph nodes in multiple locations with metabolic hyperplasia; multiple foci of metabolic hyperplasia in the right iliac bone, right acetabulum, left pubic bone and bilateral femur, above considered malignant with possible lymphoma infiltration (Fig. 2). A percutaneous splenic aspiration biopsy was performed under ultrasound localization. The bone marrow biopsy suggested heterogeneous hyperplasia, with triple lineage hyperplasia possible and no obvious heterogeneous cells. The CD series associated with lymphoma/leukemia showed a significant decrease in the CD_4:CD_8 ratio of T-lymphocytes in the specimens sent for examination. Bone marrow karyotype 46, XY. No clonal numerical or structural abnormalities were observed.

Tuberculous meningitis diagnosed in November 2021, remission after treatment → Fever, abdominal pain, and weight loss in April 2022 → Lymphoma diagnosed in May 2022 and treatment initiated.

One week later patient's spleen pathology immunohistochemistry $CD20^+$, Pax5+, BcL-2+, BcL-6+, $CD10^-$, mum-1+, Cmyc + approx. 40%, $CD30^+$, ALK-, CyclinD1-, $CD3^-$, $CD5^-$, $CD2^-$, $CD4^-$, TIA-1-, GrB-, $CD21^+$, $CD34^-$, PCK -, Ki67+ approximately 80%. negative for EBER, no detectable BcL-2, BcL-6, MYC gene repertoire in spleen tissue, exclusion double strike lymphoma. It was consistent with diffuse large B-cell lymphoma (Fig. 3) and therefore diagnosed as HIV-associated diffuse large B-cell lymphoma of the spleen.

After diagnosis, the patient was given R-DA-EPOCH (The dose of rituximab is 375mg/m^2, used on the first day of chemotherapy; Doxorubicin 10mg/m^2, vincristine 0.4mg/m^2, etoposide mg/m^2, intravenous infusion, starting on the second day of chemotherapy, continuous use for 4 days; Cyclophosphamide 750mg/m^2 for use on day 5 of chemotherapy; Prednisone acetate tablet, 100mg, was started on day 2 of chemotherapy for 5 consecutive days) chemotherapy for 21 days in 1 cycle, plus sofosbuvir-velpatasvir against hepatitis C. The anti-tuberculosis drugs and the combination of anti-retroviral drugs remained unchanged, and oral cotrimoxazole was given to prevent Pneumocystis carinii pneumonia and toxoplasma encephalopathy.The corresponding prophylaxis against CNS tumour invasion (intrathecal methotrexate, cytarabine) was carried out according to the same criteria as in HIV-negative patients [2].

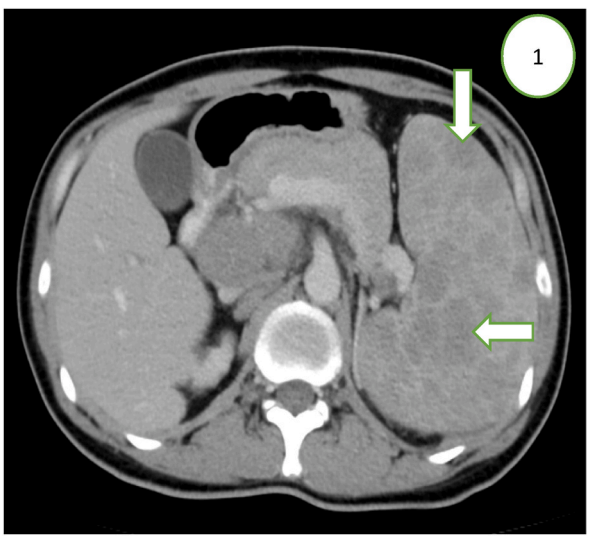

Fig. 1. Splenomegaly with multiple occupying lesions.

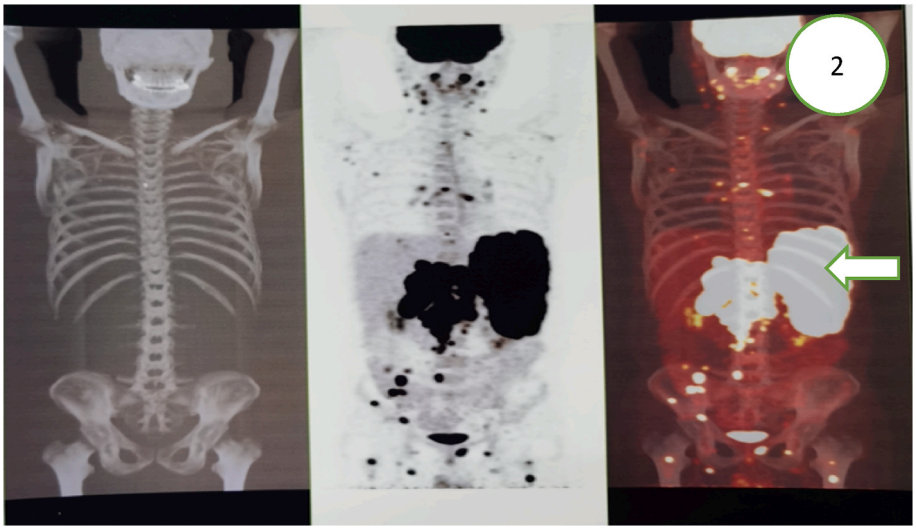

Fig. 2. PET-CT examination of splenomegaly, multiple lymph nodes at multiple sites and multiple foci of metabolic hyperplasia, with consideration of malignancy and possible lymphoma infiltration.

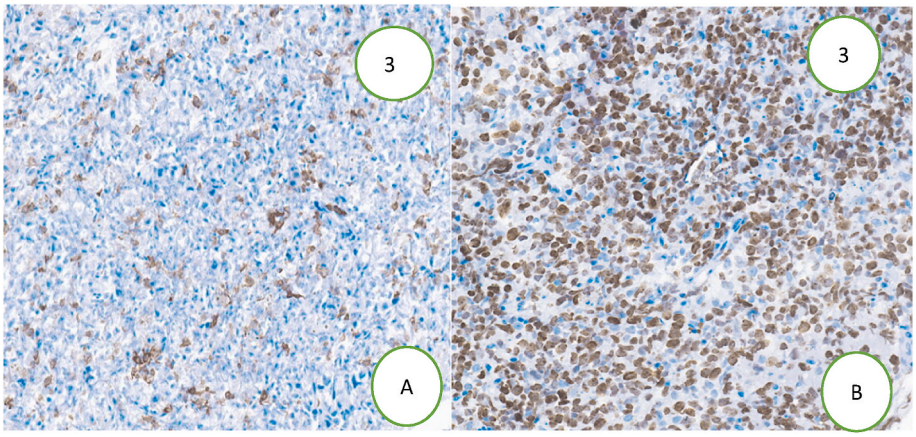

Fig. 3. ACD20+; Fig. 3B:BcL-6+。.

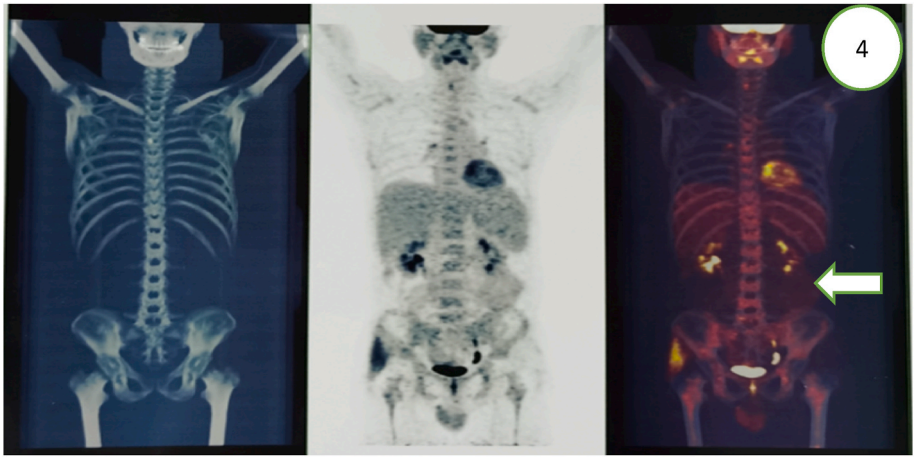

Fig. 4. PET-CT examination showed that the spleen was not large, metabolism was not high, and tumor activity was inhibited.

At the end of the first cycle of chemotherapy the patient's fever and abdominal pain resolved and the spleen was significantly reduced. At the end of the 2nd cycle of chemotherapy the patient's spleen was no longer palpable and he gained 1 kg in weight. The patient's weight was maintained at 61 kg after 4 cycles of chemotherapy. The patient experienced adverse events after chemotherapy, mainly blood routine examination indicating grade IV myelosuppression. and secondary bacterial infection, which improved with leukocyte boosting, anti-infection and transfusion of red blood cells and platelets. HCV-RNA was rechecked at weeks 4, 8 and 12 of anti-hepatitis C treatment at less than 100IU/mL, and HIV-RNA was monitored at less than 50copies/mL during this period. cerebrospinal fluid was negative for Gene-Xpert, and routine and biochemical tests were not abnormal. PET-CT at the end of the 4th cycle of chemotherapy showed no spleen enlargement, no metabolism (reduced from before); lymph nodes in multiple sites (lesions were smaller, reduced and partially disappeared); no metabolism; the above considered post-treatment changes, tumour activity was suppressed and the Deauville score was 1 (Fig. 4) and the patient is now on maintenance consolidation therapy.

3. Discussion

DLBCL is the most common histological subtype of non-Hodgkin's lymphoma, which is aggressive and highly heterogeneous in terms of clinical presentation, pathological features, treatment outcome and prognosis [3]. The patient was confirmed positive for HIV antibodies, immunocompromised, with a history of tuberculous meningitis and viral hepatitis C. Weight loss, abdominal pain and fever occurred during anti-tuberculosis treatment, and antibacterial treatment did not improve. Combined with imaging studies suggesting splenomegaly with multiple occupying lesions and possible malignant lesions, the patient was not given a puncture biopsy due to thrombocytopenia and a high risk of bleeding during clinical puncture, resulting in A definitive diagnosis was not made in time. The patient was admitted to the hospital and after obtaining the consent of the patient and family, a percutaneous percutaneous splenic puncture pathological tissue biopsy was performed under ultrasound guidance, which was an important basis for the rapid confirmation of the diagnosis in this case. Lymphoma is the most common malignant tumour of the spleen. The common findings on CT are: ①an enlarged spleen with uniform density. ②Single or multiple hypodense or isodense foci in the spleen, with mild enhancement on enhancement. ③diffuse infiltrative spleen is generally hypodense and shows heterogeneous enhancement after enhancement. To prevent bleeding after puncture, the number of punctures should be minimised and the retention time of the puncture needle in the spleen should be shortened.

Patients should consider the interactions between chemotherapy drugs, anti-tuberculosis drugs, anti-hepatitis C treatment drugs and CART drugs during lymphoma treatment. CART drugs can interact with chemotherapy drugs and may increase treatment toxicity or reduce efficacy. Among them, enhancers (ritonavir and cobicistat, etc.) may inhibit the metabolism of protease inhibitors (e.g. atazanavir, darunavir, saquinavir) and increase the toxicity of chemotherapeutic agents such as erlotinib, docetaxel and vincristine, and their concomitant use should be avoided in clinical practice; interactions between non-nucleoside reverse transcriptase inhibitors and chemotherapeutic agents may lead to reduced efficacy and should be used with caution; for example, zidovudine can cause or Zidovudine can cause or exacerbate myelosuppression and should be avoided in combination with chemotherapeutic agents that may cause myelosuppression; nucleoside reverse transcriptase inhibitors (e.g. stavudine) can cause peripheral neuropathy and should be avoided in combination with platinum, paclitaxel and vincristine alkaloids [4]. The use of hepatitis C protease inhibitors can cure hepatitis C when combined with hepatitis C virus infection, but attention needs to be paid to interactions with chemotherapeutic agents and other drugs. Rifampicin, a potent cytochrome P450 (CYP) inducer drug class, decreases the plasma concentration of sofosbuvir/velpatasvir, and clinical monitoring of blood levels is required. We monitored patients at 4, 8 and 12 weeks with HCV-RNA below the detection This suggests that anti-hepatitis C treatment is effective and further observation of anti-hepatitis C efficacy is required in later follow-up. During lymphoma treatment, the appropriate CART regimen can be selected based on drug-drug interactions or overlapping toxicity with chemotherapeutic agents, and regimens containing integrase inhibitors, which have fewer interactions with chemotherapeutic agents, are recommended [5]. Anti-tuberculosis drugs commonly used in the treatment of tumor may interfere with liver CYP450 enzyme and affect the metabolism of corresponding anti-tumor drugs. However, the mechanism of drug interaction in tumor therapy has not been fully clarified, and more theoretical and clinical data on drug interaction are needed to rationally use drugs.Six cycles of rituximab (R) plus EPOCH (etoposide, prednisone, vincristine, cyclophosphamide and adriamycin), or R–CHOP (rituximab, cyclophosphamide, adriamycin, vincristine and prednisone) has been reported as the preferred regimen for first-line treatment of HIV-DLBCL, with CHOP being similar for HIV-negative and positive The treatment effect of CHOP is similar for HIV-negative and positive DLBCL, with a complete response (CR) rate of 48%–60%, and the addition of R to CHOP increases the CR rate by about 10% [6], so the addition of R to the chemotherapy regimen is recommended to increase the CR rate. sun et al. [7] followed up 54 cases of HIV-DLBCL and found that dose-adjusted (DA) R-EPO adjusted (DA) 2-year overall survival (overall survival, OS) was 78% in the R-EPOCH group and 66% in the R–CHOP group. In addition, the incidence of CNS involvement is higher in HIV-DLBCL compared to HIV-negative DLBCL patients [2], therefore, HIV-DLBCL patients at risk of recurrent disease at the CNS site should be treated with appropriate prophylaxis (intrathecal methotrexate or cytarabine) according to the same criteria as HIV-negative patients, and a dose-adjusted regimen is recommended. In this patient's comprehensive treatment strategy, which takes into account anti-tumour, anti-HIV, anti-tuberculosis and anti-hepatitis C therapy, we chose a CART regimen that includes integrase inhibitors, and integrase inhibitors need to be dosed up when using rifampicin. After comprehensive treatment the patient's clinical symptoms resolved, the spleen shrank, and a repeat PET-CT indicated complete remission (CR), the cerebrospinal fluid was GeneXpert negative, and blood HCV-RNA and HIV-RNA were below the lower limit of detection and the treatment effect was remarkable.

In summary, when clinicians encounter immunodeficient patients with combined malignant lesions in their work, they should broaden their diagnostic thinking and need to consider rare or uncommon diseases in addition to common lesions, In particular, histopathological and immunohistochemical examinations should be carried out in time to avoid delayed treatment if the examination

suggests space-occupying lesions. In the era of CART, significant progress has been made in basic and clinical research on HIV-DLBCL. HIV-DLBCL can be treated with the same chemotherapy regimen as HIV-negative patients with adequate or intensive chemotherapy, and the same therapeutic effect as HIV-negative patients can be achieved. However, due to the interaction between CART drugs and chemotherapy drugs, the appropriate CART regimen should be chosen to minimise adverse drug reactions. There are currently few clinical trials related to HIV-DLBCL, and the use of many chemotherapy regimens and new drugs in HIV-DLBCL is somewhat limited. There is a need to further encourage and support the inclusion of HIV-DLBCL patients in clinical trials, to conduct joint multi-centre clinical trials to explore more effective treatment options, and to develop treatment plans that incorporate clinical features, co-morbidities and individualised differences in order to improve patient prognosis and increase survival expectations.

4. Conclusion

Immunodeficiency patients with spleen space occupying lesions, tuberculous meningitis, HCV infection, spleen space in addition to early biopsy diagnosis, the treatment process needs to choose the appropriate treatment plan according to the interaction between drugs, which can improve the survival time and quality of life of patients.

Informed consent

Informed consent was obtained from the patient(s) (or relative/guardian) for the publication of all images, clinical data and other data included in the main manuscript.

Author contribution statement

All authors listed have significantly contributed to the investigation, development and writing of this article.

Data availability statement

Data will be made available on request.

Additional information

No additional information is available for this paper.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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