Adult T-cell lymphoma/leukaemia with haematemesis as a prodromal manifestation

Fariba Binesh,[1] Mohamad Reza Mirjalili,[2] Hasanali Vahedian,[2] Hamidreza Bashiri[2]

[1]Department of Pathology, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[2]Department of Internal Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

Correspondence to
Dr Fariba Binesh,
binesh44@yahoo.com

SUMMARY

We report a case of adult T-cell leukaemia/lymphoma (ATLL) with haematemesis as a prodromal manifestation. The patient was a 34-year-old woman from Yazd. She also gave a history of a fluctuating skin lesions consisting of non-pruritic papules and ulcers on her feet. Upper gastrointestinal endoscopy disclosed obvious nodularities without ulceration in the antrum of the stomach. Histological and immunohistochemical studies of the gastric biopsy specimen showed lymphomatous infiltration of diffuse pleomorphic type with a T-cell phenotype. Laboratory investigations revealed leucocytosis (consisting of highly atypical lymphocytes, many with clover-leaf-shaped nuclei) and hypercalcaemia. She was found to be seropositive for human T-lymphotropic virus type 1. A diagnosis of overt ATLL was made. The findings in this case indicate that an awareness of the existence of this disease in anon-endemic area such as Yazd is necessary to avoid potential misdiagnosis and be helpful in appropriate therapeutic decision.

BACKGROUND

Human T-lymphotropic virus type 1 (HTLV-1) was the first oncogenic human retrovirus discovered in 1980. HTLV-1 is present throughout the world with clusters of high endemicity including mainly southern Japan, the Caribbean region, parts of South America and intertropical Africa. In the high endemic areas, 0.5–50% of the people have antibodies against HTLV-1 antigens. HTLV-1 seroprevalence increases with age, especially in women. HTLV-1 has three modes of transmission: mother to child, mainly through prolonged breast feeding (>6 months); sexual, predominantly occurring from male to female; and by contaminated blood products containing infected lymphocytes. HTLV-1 is mainly the aetiological agent of two very severe diseases: a malignant T-CD4 cell lympho proliferative disorder with a very poor prognosis, named adult T-cell leukaemia/lymphoma (ATLL), and a chronic neuro-myelopathy named tropical spastic paraparesis/HTLV-1-associated myelopathy. HTLV-1 is also associated with rare anterior uveitis, infective dermatitis and myositis in some high HTLV-1 endemic areas.[1] ATLL is essentially a disease of adults, characterised clinically by generalised lymphadenopathy, hepatosplenomegaly, skin lesions and hypercalcaemia. Here, we report a rare case of ATLL presented with haematemesis as a prodromal manifestation. This case report shows that an awareness of the existence of this disease in non-endemic area is necessary to avoid potential misdiagnosis.

CASE PRESENTATION

A 34-year-old woman was referred from a community hospital to our hospital, with haematemesis. She had no remarkable medical history and previous transfusion. Physical examination revealed a febrile (her body temperature was 38°C), some lethargic young woman. She had generalised, but small, lymphadenopathy, mild hepatosplenomegaly and red papules on both feet (figure 1).The patient denied intravenous drug consumption and travel outside the Yazd.

INVESTIGATIONS

Owing to haematemesis, she underwent upper gastrointestinal endoscopy. Upper gastrointestinal endoscopy disclosed obvious nodularities without ulceration in the antrum of the stomach. Histological and immunohistochemical studies of the gastric biopsy specimen showed lymphomatous infiltration of diffuse pleomorphic type with a T-cell phenotype (figures 2–5). The white-cell count was 25×10^9/litre, with 80% lymphocytes (consisting of highly atypical lymphocytes, many with clover-leaf-shaped nuclei). The serum biochemistry test results were as follows: total protein, 5 g/dl (reference range, 6.7–8.3 g/dl), albumin 2.5 g/dl (reference range 3.8–5.3 g/dl), total bilirubin 1 g/dl (reference range=0.2–1.1 g/dl), asparatate aminotransferase=35 IU/l (reference range=10–40 IU/l), alanine aminotransferase=34 IU/l (reference range=5–45 IU/l) and low-dose heparin=500 IU/l (reference range=115–245 IU/l). Serum ferritin level was 150 ng/ ml (reference range, 5–152 ng/ ml), and the serum calcium concentration was 13 mg/dl (normal value=8.3–10.3 mg/dl). Blood urea nitrogen was 60 mg/dl, and serum creatinine was 3.5 mg/dl. Abdominal sonography showed hepatosplenomegaly and enlarged kidney. A bone marrow aspirate showed scattered infiltration of mentioned lymphoid cells. Peripheral blood flow cytometry showed

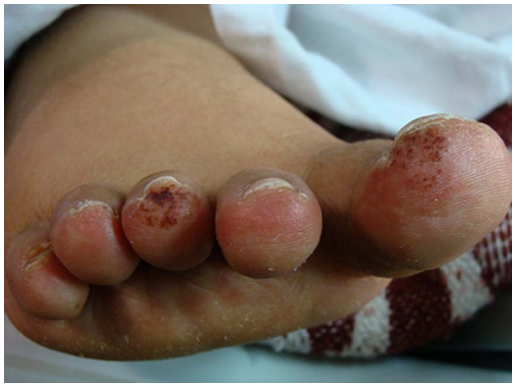

Figure 1 Gross photograph shows red papules on patient's foot.

To cite: Binesh F, Mirjalili MR, Vahedian H, *et al*. *BMJ Case Reports* Published online: 29 November 2012 doi:10.1136/bcr-2012-006957

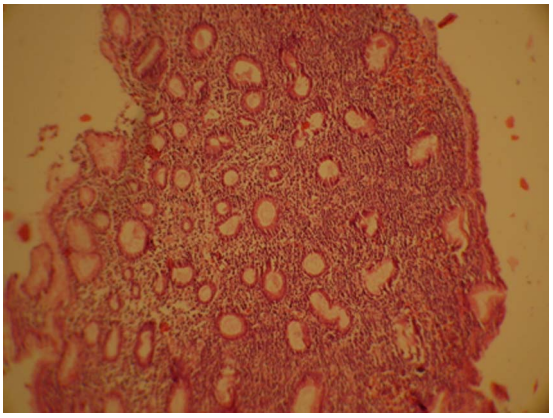

Figure 2 Section shows gastric mucosa with lymphomatous infiltration of diffuse pleomorphic type (H&E ×10).

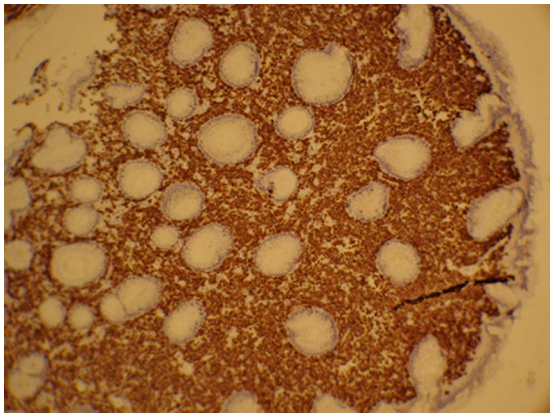

Figure 4 Section shows that lymphomatous cells are CD 3-positive (IHC staining ×10).

that atypical lymphoctes were positive for CD2, CD3, CD4, CD5 and CD25 and negative for CD7. Her anti-HTLV-1 antibody was positive. The diagnosis was overt ATLL.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of ATLL includes other mature T-cell neoplasms such as T-cell prolymphocytic leukaemia (T-PLL), Sezary syndrome, peripheral T-cell lymphomas and occasionally healthy carriers of the virus or Hodgkin disease.[2]

TREATMENT

The hypercalcaemia resolved rapidly after treatment with fluids and biphosphonates. The patient received CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone), hyper CVAD (cyclophosphamide, vincristine, doxorubicin and dexamethasone) and also received intrathecal chemotherapy (MTX, cytarabine).

OUTCOME AND FOLLOW-UP

Several weeks later, the patient was afebrile, and the physical examination showed a decrease lymphadenopathy and skin lesions. The liver and spleen were no longer palpable. Levels of calcium, lactate dehydrogenase, blood urea nitrogen and creatinine were normal as was the white-cell count; the patient was in remission and all tumour masses had disappeared, as assessed by clinical examination and abdominal CT scan. We are currently planning bone marrow transplantation.

Serum specimens were obtained from10 family members of the patient. One person, (her mother) had an antibody against HTLV-I. She lived all her life in Yazd, had no history of blood transfusions, and she did not use any intravenous drugs.

DISCUSSION

A case of ATLL associated with HTLV-1 with haematemesis as a prodromal manifestation has been reported from Yazd. ATLL is a lymphoproliferative neoplasm of helper T-lymphocytes caused by HTLV-1. The disease was first described in Kyushu, in southwestern Japan. HTLV-1 is a retrovirus, which means that these viruses do not contain genetic material made of DNA, but instead carry RNA. These viruses only infect T cells. Only 2–5% of patients infected with the HTLV-1 virus will eventually develop ATLL. Currently, physicians are unable to predict which infected patients will develop ATLL. The most important route is vertical transmission by breast-feeding.[3] In this particular case, we were unable to find out how her mother became infected by this virus.

The median age of diagnosis is 58 years, partly explained by the long latency period between infection and development of ATLL, which can range from 10 to 30 years.[4] Our patient was a 34-year-old woman. The distribution of ATLL is typically systemic. In addition to peripheral blood and lymph nodes, the disease also affects other parts of body such as the skin, lung, liver, gastrointestinal tract, and central nervous system.[5] The

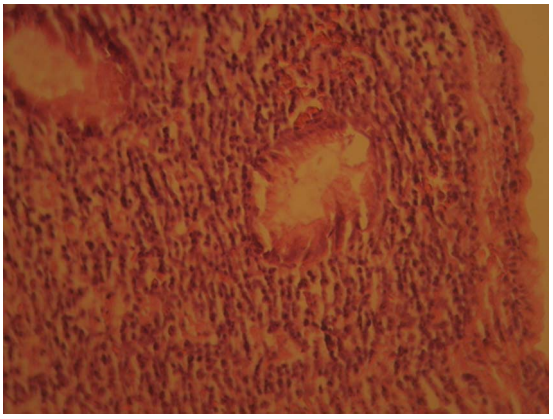

Figure 3 Section shows gastric mucosa with lymphomatous infiltration of diffuse pleomorphic type (H&E ×40).

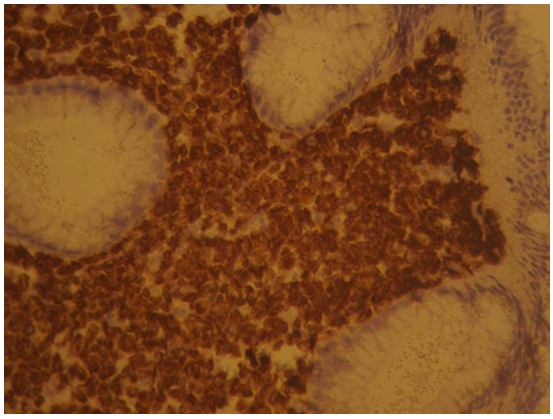

Figure 5 Section shows that lymphomatous cells are CD 3-positive (IHC staining ×40).

diagnosis should be based on a constellation of clinical features and laboratory investigations.

Our patient was admitted as a result of haematemesis but during the physical examination, skin lesions, generalised lymphadenopathy and hepatosplenomegally were also evident. Several clinical variants of this disease, including acute, lymphomatous, chronic and smouldering ATLL, have been described to date.[6] The acute-type ATLL is the most common variant and is characterised by a leukaemic phase, typically with a noticeably high white blood cell count, skin rash and widespread lymphadenopathy. The present case appears to be a typical ATLL subtype. ATLL is usually a malignancy of CD4 T regulatory cells, although suppressor activity may be lacking, and occasional examples of CD8 lymphoid malignancy have also been described.[7–9] However, rare cases of an unusual form of immunophenotype characterised by coexpression of CD4+CD8+ double-positive cells have been reported.[10] Flowcytometry, in our case, showed that the neoplastic cells were positive for CD2, CD3, CD4, CD5 and CD25 and negative for CD7. The clinical course is aggressive with a median survival of less than 12 months in the acute and lymphomatous forms. Despite major advances in understanding the pathogenesis of the disease, management of these patients remains a challenge for clinicians as they do not respond or achieve only transient responses to therapies used in high-grade lymphomas. The use of antiretroviral agents such as zidovudine in combination with interferon α, with or without concomitant chemotherapy, has shown activity in this disease with improvement in survival and response rate.[2] Its poor prognosis is mainly due to resistance to chemotherapy.[11] The median survival is 5 months in patients with the acute type and 10 months in patients with the lymphomatous type.[12] Although the smouldering and chronic types have a better prognosis, no treatment has halted their progression to the acute type.[5] The present case received chemotherapy and she is in remission now. In conclusion, an awareness of the existence of this disease in a non-endemic area, such as Yazd, is necessary to avoid potential misdiagnosis and to facilitate therapeutic decision.

Learning points

- The clinical manifestations of adult T-cell leukaemia/lymphoma are typically systemic.
- An awareness of the existence of this disease in non-endemic area is necessary to avoid potential misdiagnosis and be helpful in appropriate therapeutic decision.
- Despite major advances in understanding the pathogenesis of the disease, management of these patients remains a challenge for clinicians.
- Patients do not respond or achieve only transient responses to therapies used in high-grade lymphomas.

Competing interests None.

Patient consent Obtained.

REFERENCES

1 Gessain A. Human retrovirus HTLV-1: descriptive and molecular epidemiology, origin, evolution, diagnosis and associated diseases. *Bull Soc Pathol Exot* 2011;104:167–80.
2 Yagi T, Ishikawa J, Aono N, , *et al*. Epstein–Barr virus-associated post-transplant lymphoproliferative disorders after allogeneic peripheral blood stem cell transplantation for Hodgkin-like adult T-cellleukemia/lymphoma. *Int J Hematol* 2012;95:214–16.
3 Evans AS, Kaslow R. *Viral infections of humans*. New York: Plenum Medical Press, 1997:785–813.
4 Tajima K. The 4th nation-wide study of adult T-cell leukemia/lymphoma (ATL) in Japan: estimates of risk of ATL and its geographical and clinical features. The T- and B-cell Malignancy Study Group. *Int J Cancer* 1990;45:237 e43.
5 Bunn PA Jr, Schechter GP, Jaffe E, *et al*. Clinical course ofretrovirus-associated adult T-cell lymphoma in the United States. *N Engl J Med* 1983;309:257–64.
6 Shimoyama M. Diagnostic criteria and classification of clinicalsubtypes of adult T-cell leukaemia-lymphoma. A report from the Lymphoma Study Group (1984–87). *Br J Haematol* 1991;79:428–37.
7 Yano H, Ishida T, Inagaki A, *et al*. Regulatory T-cell function of adult T-cell leukemia/lymphoma cells. *Int J Cancer* 2007;120:2052–7.
8 Abe M, Uchihashi K, Kazuto T, *et al*. Foxp3 expression on normal and leukemic CD4(+)CD25(+) T cells implicated in human T-cell leukemia virus type-1 is inconsistent with Treg cells. *Eur J Hematol* 2008;81:209–17.
9 Shimauchi T, Kabashima K, Tokura Y. Adult T-cell leukemia/lymphoma cells from blood and skin tumors express cytotoxic T lymphocyte-associated antigen-4 and Foxp3 but lack suppressor activity toward autologous CD8+ T cells. *Cancer Sci* 2008;99:98–106.
10 Pombo De Oliveira MS, Loureiro P, Bittencourt A, *et al*. Geographic diversity of adult T-cell leukemia/lymphoma in Brazil. The Brazilian ATLL Study Group. *Int J Cancer* 1999;81:1–8.
11 Shimoyama M. Treatment of patients with adult T-cell leukemia-lymphoma: an overview. *Gann Monogr Cancer Res* 1992;39:43–56.
12 Kawano F, Yamaguchi K, Nishimura H, *et al*. Variation in the clinical courses of adult T-cell leukemia. *Cancer* 1985;55:851–6.