

CASE REPORT

A 61-year-old woman with adult T-cell leukemia/lymphoma

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Abstract

Adult T-cell leukemia/lymphoma (ATL) is caused by human T-cell lymphotropic virus type-1 (HTLV-1) infection. Classification of ATL includes acute, chronic, lymphomatous and smoldering, and main features are hypercalcemia, organomegaly, bone, brain, lung, and skin changes. Elevated mortality rates of ATL may be due to the advanced age at diagnosis, because this malignancy can evolve unsuspected for decades before the first clinical manifestations. Palliative therapy, chemotherapy and stem cell transplantation are often utilized, but response to treatment is poor. The patient herein reported presented diffuse abdominal pain with duration of eight months in addition to ascites. The diagnosis of the acute leukemia type of ATL was done with base on clinical, laboratory and imaging findings. Gastrointestinal symptoms and ascites are uncommon first manifestations of ATL, and pose challenging diagnosis.

Keywords: adult T-cell leukemia/lymphoma, ATL, human T-cell lymphotropic virus type-1, HTLV-1.

Introduction

The case herein reported is about a woman with adult T-cell leukemia/lymphoma (ATL) caused by human T-cell lymphotropic virus type-1 (HTLV-1) infection of CD4 T-cells [1–7]. She presented mesenteric and retroperitoneal lymph node enlargement, and malignant ascites. ATL was described for the first time in 1977 and has high mortality rates, in part due to the advanced age at diagnosis related to latent periods of decades [1, 2, 5, 7]. Age over 40 years, high levels of urea, lactate dehydrogenase (LDH) and calcium, and low albumin are bad prognostic factors [2, 5, 7]. Clinical classification of ATL includes acute, chronic, lymphomatous and smoldering [1–5]. Main features are hypercalcemia, organomegaly, bone, brain, lung, and skin changes [1–7]. Management options include palliative therapy, chemotherapy and stem cell transplantation. Clinically manifested ATL has rapid progress, and death often occurs within one year [1, 2]; physiopathology is not totally clarified, and response to treatment is usually poor [1, 2, 5, 7]. Autopsies have found involvement of stomach, small and large intestine in ATL patients [6]. Hepatomegaly, splenomegaly and ascites can be secondary to organ infiltration by ATL [4]. As ascites and gastrointestinal symptoms are seldom reported, the authors believe that extrapolated data from case studies of ATL are useful to the knowledge about this condition [6].

Case presentation

A 61-year-old chagasic woman was admitted because of abdominal distension associated with diffuse pain since eight months ago. She was previously submitted to virtual colonoscopy and upper digestive endoscopy, which revealed redundant colons, small hiatal hernia, and mild

erosive esophagitis (Figure 1). Furthermore, the phenotype evaluation performed in peripheral lymphocytes of blood and bone marrow samples revealed the expressions of CD3, CD4, CD25, and CD45, without the expressions of CD7, CD8 and CD20. Studies of gastric biopsy showed mild neutrophilic activity, follicular hyperplasia with lymphoid aggregates and absence of *H. pylori*. Laboratory routine tests (with normal values in parenthesis) and respective controls are showed in Table 1.

Table 1 – Laboratory routine and controls of a 61-year-old woman with adult T-cell leukemia/lymphoma

Parameters (normal ranges)	αD1	D5	D9	D13	D17	D20	ωD35
Hemoglobin (13.5–18 g/dL)	14.8	17.2	16.4	15.6	15	14.7	8.8
Hematocrit (42–52%)	43.7	49.7	47.4	47.5	44.4	42.6	24.5
Leukocytes (4–11×10 ⁹ /L)	15.4	17.9	22.7	25.5	31	42.2	16.8
Neutrophils (40–70%)	58	54	58	60	46	57	74
Lymphocytes (1–3.5×10 ⁹ /L)	4.5	7.6	7.7	10	13.6	14.8	4.1
Platelets (140–450×10 ⁹ /L)	365	406	543	736	695	603	72
Albumin (3.5–4.5 g/dL)	3.6	3.5	–	3.2	–	–	1.9
C-RP (0.5–0.9 mg/dL)	–	4.6	7	20.5	4.6	5.6	12.9
Sodium (135–145 mmol/L)	141	137	137	131	135	141	148
Potassium (3.5–5.2 mmol/L)	4	4.2	4.6	4.2	4.4	4.6	3.9
AST (<32 IU/dL)	31.5	32	49.7	41.7	13	31.8	65.7
ALT (<33 IU/dL)	19.4	18.4	22.5	24.3	32.7	21.8	10.9
LDH (240–480 IU/L)	–	725	–	–	635	–	–

Parameters (normal ranges)	α D1	D5	D9	D13	D17	D20	ω D35
GGT (5–36 IU/L)	34	133	646	1598	1051	–	–
Urea (10–50 mg/dL)	36.8	30.4	49.5	87.9	59.8	49.6	102.9
Creatinine (0.6–1.3 mg/dL)	0.9	0.9	1.4	1.6	0.9	0.9	1.3
Ionized calcium (1.1–1.35 mmol/L)	–	–	–	–	–	1.47	1.49

α D1: September 23rd, 2015; ω D35: Death; C-RP: C-reactive protein; AST: Aspartate transaminase; ALT: Alanine transaminase; LDH: Lactate dehydrogenase; GGT: Gamma-glutamyl transferase; Abnormal data are in bold.

Determinations of tumor markers revealed: α -fetoprotein 3.78 (0.5–5.8) IU/mL, CA 19-9 10.49 (<34) IU/mL, CA 125 283.3 (<35) IU/mL, CEA 0.965 (<5) ng/mL, and β_2 -microglobulin 4.24 (1.09–2.53) mg/L. Results of the serological panel for viral agents was unremarkable, except

for high sample-to-cutoff (s/co) ratio on chemiluminescent immunoassay for HTLV-1 [103.57 (<1) s/co], strongly consistent with diagnosis of this infection. Images of computed tomography with contrast of thorax and abdomen revealed multiple lymph node enlargements with confluence in mesenteric and retroperitoneal regions, moderate ascites and left pleural effusion with atelectasis, and signs of bronchitis (Figure 2). On D6, samples of paracentesis revealed a cloudy effusion with 87% mononuclear cells, proteins 2.79 g/dL, albumin 1.8 g/dL, glucose 103 mg/dL, and LDH 425 IU/dL; cultures for microorganisms were negative; oncotic cytology showed high number of atypical non-aggregated cells of small diameter and lymphoid aspect, permeated by plasmocytes, scarce neutrophils and red cells. Worthy of note, was the finding of circulating T-lymphocytes with polylobate nuclei in addition to typical “flower cell” features (Figure 3).

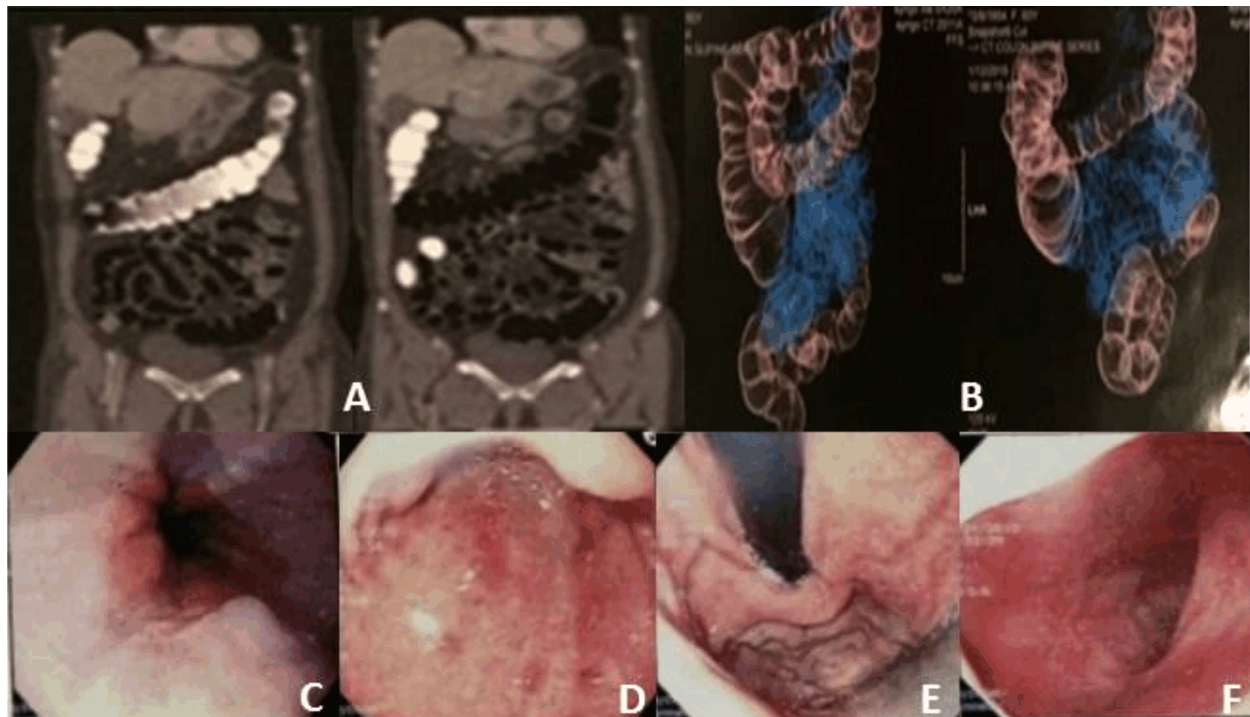


Figure 1 – Virtual colonoscopy and upper digestive endoscopy. (A and B) Redundant colons consistent with chagasic megacolon; (C and D) Mild erosive esophagitis; (E and F) Small hiatal hernia.

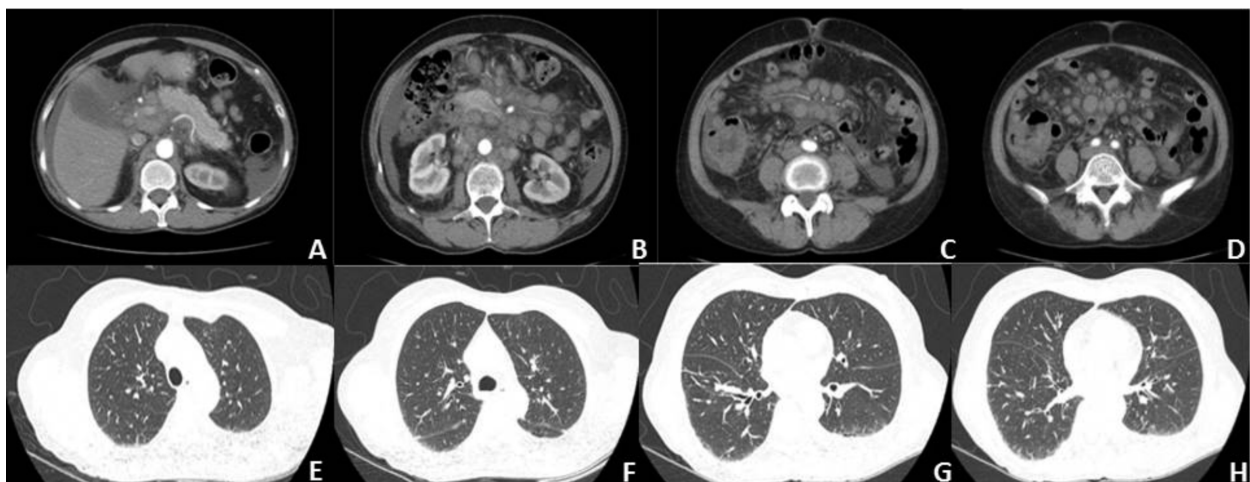


Figure 2 – Computed tomography with contrast. (A–D) Images of abdomen showing multiple lymph node enlargements with confluence in mesenteric and retroperitoneal areas, and moderate ascites without organomegaly; (E–H) Images of thorax revealing left pleural effusion, linear atelectasis, and signs of bronchitis.

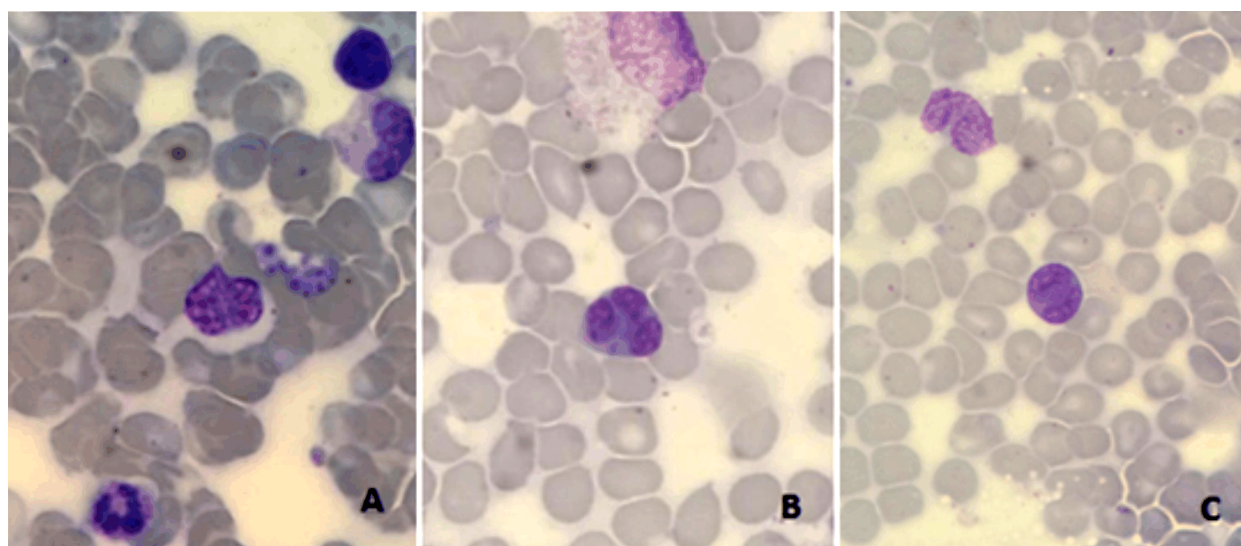


Figure 3 – (A and B) T-lymphocytes with polylobate nuclei and “flower cell” features, strongly consistent with the diagnosis of ATL; (C) Lymphocyte with nuclear atypia.

As a whole, these morphological characteristics were considered strongly consistent with the diagnosis of ATL. Paracentesis done on D14 revealed a milky fluid with 500 red cells, 3400 nucleated cells, 85% mononuclear, proteins 2.56 g/dL, albumin 1.63 g/dL, glucose 120 mg/dL, LDH 534 IU/dL, total cholesterol 64 mg/dL, triglycerides 154 mg/dL, characterizing a chylous ascites. As a whole, her clinical and complementary data were consistent with diagnosis of ATL associated with HTLV-1 infection. The patient was referred to Hematology and underwent prophylactic antibiotic therapy with sulphamethoxazole-trimethoprim and metronidazole plus treatment for HTLV-1 with AZT and pegylated interferon. She evolved in poor general clinical condition, severe breathlessness, and intestinal semi-occlusion. Hence, on D34 she was transferred to Intensive Care and treated with orotracheal intubation and vasoactive drugs. Notwithstanding, her death occurred on the next day due to multiple organs failure.

Discussion

ATL is a challenging malignancy first described in 1977, affecting up to 5% of people infected by HTLV-1 [1]. The incidence is higher in Japan, Caribe, Central and South America, Western Africa, Iran, and Southeast USA; the very aggressive acute and lymphoma ATL are the most often described types, and have the poorest prognosis [5, 7]. Acute ATL is synonymous of leukemia and is characterized by more than 4000 circulating lymphocytes, with 5% clonal T-cells, and either LDH more than twice upper normal level, or calcium equal or higher than 11 mg/dL [7]. Diagnostic pitfalls are often related to the unspecific clinical manifestations and the long period of latency [1, 7]. Yared & Kimball commented new agents for management of patients with ATL, including brentuximab vedotin, bortezomib, lenalidomide, and IL2 fused with the diphtheria toxin targeting CD25, pralatrexate, among others; nevertheless, the authors called attention to the fact that actually there is no consensus guideline for treatment [7]. Worthy of note, the increasing number of allogenic stem cell transplantations has decreased the mortality rate [5].

With base on the clinical and prognostic criteria of Shimoyama, Kawano *et al.* described 99 patients with ATL. They were distributed in the following types: acute (47.4%), lymphoma (32.3%), chronic (11.1%), and smoldering (9.1%) [1]. Aggressive ATL occurred in 81 patients and required treatment (acute and lymphoma types, and two of chronic type); the age range was 34–93 years with a median of 67.5 years, and 56.8% of individuals were female [1]. The authors commented the favorable role of early diagnosis and prompt utilization of mogamulizumab-combined chemotherapy followed by reduced-intensity hematopoietic stem cell transplantation in elderly people with ATL [1]. Khader *et al.* described four (80%) men and one woman with ATL and presenting cutaneous changes, including umbilicated and verrucous papules, annular plaques, nodules, and hypopigmented and purpuric macules. The patients were distributed in the following ATL types: acute (40%), lymphoma (20%), chronic (11.1%), and smoldering (20%); the age range was 30–62 years with a median of 52 years, and mean age of 46.8 ± 14.9 years [2]. The authors highlighted the need to be aware about possible multifaceted cutaneous changes related to ATL [2]. Popescu *et al.* reported a 34-year-old patient with abdominal pain due to acute pancreatitis, and laboratory data were hypercalcemia, elevated LDH, AST, ALT, urea and creatinine; and accentuated lymphocytosis (22.7×10^9); furthermore, the HTLV-1 test was positive, and the histopathological evaluation of bone marrow confirmed ATL [3]. The authors emphasized the rarity of this abdominal onset in ATL patients and commented the role of elevated calcium levels in the origin of pancreatitis, and hypothesized a pancreatic infiltration by abnormal lymphocytes [3]. Shimamura *et al.* reported abdominal ultrasonography findings from 40 patients with the four types of ATL [4]. Hepatosplenomegaly was more frequent in the acute and lymphoma types due to organ infiltration by ATL cells; and lymph node enlargement was very common in the lymphoma type but was rarely found in the other types [4]. The occurrence of ascites and pleural and pericardial effusions was restricted to the acute and lymphoma types [4]. In concordance with those studies, uncommon abdominal manifestations were the hallmark of the present report.

In this setting, an initial concern was about gastrointestinal involvement secondary to systemic ATL, as commented by Vetro *et al.* in their recent review of endoscopic investigation on rare gastrointestinal lymphomas [6]. Without any specific endoscopic pattern, stomach (40%), small intestine (38%), and colon (34%) are involved, and this uncommon localizations reflect the degree of ATL severity and may have negative impact in the outcomes [6]. There is a relationship between *Helicobacter pylori* infection and the gastric malignant lymphocyte infiltration [6]; however, in the case herein reported, lymphoid aggregates occurred without cell atypia and in absence of *H. pylori*. As necropsy study was not performed, the hypothesis of gastroduodenal involvement could not be entirely excluded.

The diagnosis of ATL in the >60 aged woman herein reported was characterized by the evidence of typical “flower tree” lymphocytes, in addition to lower albumin (1.9 g/dL), hypercalcemia (1.49 mmol/L), and elevated blood levels of LDH (725 IU/L), urea (102.9 mg/dL), creatinine (1.6 mg/dL), and β_2 -microglobulin (4.24 mg/L). Anemia, leukocytosis, thrombocytosis, and high levels of C-RP (20.5 mg/dL) and GGT (1598 IU/L) also occurred. Conspicuous enlarged abdominal and retroperitoneal lymph nodes were detected, lymphocyte counts in peripheral blood surpassed $4 \times 10^9/L$; in addition, circulating clonal T-cells were found, indicating the leukemia type [5, 7]. As a whole, the finding of high counts of leukocytes and lymphocytes; circulating “flower cells”; elevated LDH and BUN (blood urea nitrogen); hypercalcemia; ascites and pleural effusion; pulmonary changes; and absence of involvement of the spleen, liver or skin, were considered consistent with the acute clinical subtype of ATL [1–7]. The phenotype evaluation of peripheral blood and bone marrow lymphocytes revealed expression of CD3, CD4, CD25, and CD45, whereas CD7, CD8 and CD20 were negative; accordingly to literature, the diagnostic criteria of acute ATL were fulfilled [2, 3, 5, 7]. In this setting, one should cite the complete remissions of ATL obtained with the novel anti-CD25 recombinant immunotoxin LMB-2 and chemotherapy with fludarabine and cyclophosphamide to block immunogenicity [8]. Therefore, prophylactic antibiotic therapy associated with AZT and pegylated interferon was promptly administered; notwithstanding, the patient died before undergoing the scheduled conventional cytotoxic chemotherapy courses [7].

Conclusions

Considering that adult T-cell leukemia/lymphoma is an aggressive condition poorly responsive to chemotherapy, one must emphasize the role of reduction in the number of HTLV-1 carriers, in addition to early diagnosis, which can allow immediate beginning of treatment and palliative care, aiming better quality of life for affected patients. The authors strongly believe that the role played by the immunophenotyping of peripheral blood and medullary blood, in addition to virological evaluation, must be emphasized for establishment of correct diagnosis of ATL.

Conflict of interests

The authors declare that they have no conflict of interests.

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