Adult T-cell Leukemia/Lymphoma: First case report from Qatar

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Abstract:

In what appears to be the first case of Adult T-cell Leukemia/Lymphoma (ATLL) reported in Qatar and Middle Eastern Arab countries, a 39-year-old lady presented first with Pneumocystis carinii pneumonia and hypercalcaemia and later showed the full picture of ATLL, splenomegaly leukocytosis, skin rash, and bone marrow infiltrations. She responded well to chemotherapy, with complete remission after four cycles of combination chemotherapy but the prognosis of patients with ATLL is poor. Although patients may respond initially to treatment with combination chemotherapy regimens devised for advanced, aggressive Non-Hodgkin’s Lymphoma (NHL), relapses are common with a median survival of eight months and a four-year survival of 12 percent.

Key words: Adult T-cell leukemia/lymphoma, HTLV-1, Pneumocystis carinii pneumonia, Hypercalcaemia

Introduction:

According to the REAL and WHO classifications adult T-cell lymphoma/leukemia (ATLL) is a peripheral T-cell neoplasm associated with infection by the human T-lymphotropic virus, Type I (HTLV-I)(1,2). It is a highly aggressive T-cell non-Hodgkin’s lymphoma (NHL) variant. The most common presentation of ATLL is an acute onset bone marrow and peripheral blood involvement with a high white blood cell count and circulating lymphocytes with highly abnormal convoluted nuclei, hypercalcaemia, lytic bone lesions, cutaneous lesions (often simulating those seen in mycosis fungoides), generalized lymphadenopathy, hepatosplenomegaly, interstitial pulmonary infiltrates and central nervous system involvement in some patients.

ATLL is sub-classified into four groups: acute, lymphomatous, chronic and smouldering. The acute form typically involves multiple organs (including the central nervous system), the skin, a leukemic peripheral blood picture, hepatosplenomegaly and systemic lymphadenopathy. Lytic bone lesions are often present with hypercalcaemia. The peripheral blood leukemic cells are multilobated lymphocyte “flower cells,” with a T-helper cell immunophenotype and expression of CD2, CD3, CD4, CD5 but not CD8. CD7 expression is often lost. The strong expression of CD25 (interleukin-2 receptor) is characteristic of ATLL and helps to distinguish this disorder from cutaneous T-cell lymphoma(3). The prognosis is poor, although patients may respond initially to treatment with combination chemotherapy regimens devised for advanced, aggressive NHL. Relapses are common, with a median survival of eight months and a four-year survival of 12 percent(4,5).

Case presentation:

A 39-year-old Iraqi female, married with one child, a history of one abortion, not known to have chronic illness, was admitted to Hamad General Hospital with a dry cough, pleuritic chest pain, shortness of breath of three weeks duration and no fever. The physical examination was normal apart from bilateral lower chest crepitations. Chest x-ray showed bilateral lower zone infiltrations and Complete Blood Counts (CBC) showed leukocytosis. Urine electrolytes showed elevated serum calcium 2.8 mmol/l. Echo showed mild to moderate pericardial effusion. She was treated for community-acquired pneumonia (CAP).

Three days later she deteriorated and was moved to the medical intensive care unit (MICU) where CT scans of chest and abdomen showed diffuse bilateral areas of ground-glass appearance with bronchietatic changes suggestive of acute diffuse interstitial lung disease; the abdomen was normal. Tests for antinuclear antibodies (ANA) were negative for C3 and normal for C4. Elective intubated bronchoscopy with bronchio-alveolar lavage (BAL) was positive for pneumocystis carinii (PCP). She was treated accordingly (co-trimoxazole (Septrin; GlaxoSmithKline) and with a diagnosis of PCP plus hypercalcaemia she was discharged 18 days after admission on co-trimoxazole and tapering doses of prednisolone.

Four days after discharge she was re-admitted to MICU as a case of hypercalcaemia with nausea, vomiting, polyuria and polydipsia. Serum calcium was 4.29 mmol/l, phosphorus was
0.71 mmol/l. She was given pamidronate, hydrocortisone and calcitonin. A peripheral blood smear showed atypical lymphocytes with folded nuclei. Bone marrow (BM) showed no evidence of lymphoma involvement. CT scans of chest and abdomen showed clearance of the bilateral basal infiltration and an enlarged lymph node in the pelvis. Bone scans suggested generalized metabolic bone disease.

One month later she was referred to Hematology/Oncology at a time when she was asymptomatic, in fair general condition with no skin rash. Her spleen was palpable 4 cm below the left costal margin. When seen in the clinic two weeks later she had a maculopapular skin rash (Figure 1) on the abdomen and chest, and the spleen was palpable 6 cm below the left costal margin. Complete Blood Counts, White Blood Cell, 22.6 x 10^9/L, hemoglobin 118 gm/L, platelets 170 x 10^9/L, LDH 371 iu/L, and serum calcium 2.64 mmol (Figure 3). A peripheral blood smear showed many circulating atypical lymphocytoid cells with convoluted hyperlobulated nuclei, some cribriform, and dark blue cytoplasm (Figure 4). Bone marrow aspiration and biopsy showed diffuse infiltration of the marrow by lymphoid mononuclear cells with convoluted nuclei variable in size and shape; some areas showed fibrosis (Figure 5). Immunohistochemistry on bone marrow showed positive CD3, CD4, and CD5 and negative CD20 and CD34.

Flowcytometry showed positive CD3, CD4 and CD25 and negative CD7, CD8, CD11c, CD19 and CD23 (Figure 7). A skin biopsy showed a perivascular dermal infiltrate of atypical lymphoid cells with large hyperchromatic folded nuclei, also seen inside dermal blood vessels (Figures 6A and B).

The patient was started on CHOP chemotherapy (cyclophosphamide 750 mg/m², doxorubicin 50mg/m², Vincristine 1.4 mg/m² and prednisolone 100 mg/day) with intrathecal methotrexate at each cycle. After the fourth cycle...
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Figure 5: BM trephine biopsy shows interstitial infiltration by highly pleomorphic small, medium and large lymphoid cells with prominent nuclear membrane irregularity. Few residual normal cells seen. H&E x 1000. The cells were strongly positive for CD3 (left inset) and CD4 (right inset) x 1000.

Figure 6: Skin biopsy from abdominal wall NM1. A medium power and high power view of the H&E stained skin biopsy showing superficial and mid dermal infiltrate of atypical lymphoid cells and sparing the overlying epidermis.

Figure 7: Flow cytometry immunophenotyping - The lymphoma cells (black arrow) show characteristic positivity for CD3, CD5, CD4, CD25 and negative CD7.
she had complete clinical and hematological remission (no skin rash, spleen no longer palpable, normal CBC and bone marrow aspiration and biopsy). The intention is for her to receive two more cycles of chemotherapy and then a transplantation of autologous peripheral stem cells.

**Discussion:**

Infection with the human T-cell lymphotropic virus Type I, a retrovirus, can cause a distinctive hematological malignant disease, adult T-cell leukemia-lymphoma. The human T-cell lymphotropic viruses Type I and II (HTLV-1/HTLV-II) belong to a group of oncogenic retroviruses known to be pathogenic to man. HTLV-I was discovered in 1980 and was shown to be associated with the etiology of adult T-cell leukemia/lymphoma (ATLL), a progressive autoimmune-like neurological disorder known as tropical spastic paraparesis or HTLV-I associated myelopathy and autoimmune-like rheumatic disorders.

HTLV-1 was known to be endemic in certain Afro-Caribbean countries and in Europe and America the virus is more commonly found in populations that have emigrated from such endemic areas.

Adult T-cell leukemia-lymphoma is etiologically linked to the human T-cell lymphotropic virus Type I (HTLV-I). HTLV-I, a retrovirus, is endemic in southern Japan and the Caribbean basin and occurs sporadically in Africa, Latin America, the Middle East, and the United States. Adult T-cell leukemia-lymphoma occurs in less than five percent of people with HTLV-I infection, with an average latency period of more than 30 years. A cellular immune deficiency in affected patients allows opportunistic infections to develop.

In the State of Qatar screening for HTLV-I commenced in August 1991 and the modified screening assays that include screening for both HTLV-I and HTLV-II were adopted as soon as they became available in 1997 although it is not possible to work out the actual prevalence of HTLV infection among our donors. There are few reports from the Middle East about the prevalence of HTLV virus infection and no case of adult T-cell leukemia/lymphoma. The case we are reporting had positive HTLV-1 antibodies detected by ELISA and confirmed by the Western Blot test but tests on her husband and son in Qatar were negative. She presented with PCP and hypercalcemia, and bone marrow aspiration and biopsy showed no evidence of lymphoid involvement, but within two months she developed other features of the disease, organomegaly, skin rash, leukocytosis and bone marrow infiltration.

This is a rare form of presentation. Several variants have been described depending upon the clinical features: acute, lymphomatous, chronic and smoldering, and appear to have differing genomic alterations. The most common presentation of ATLL, occurring in about 60 percent of cases, is one of acute onset with classical features of bone marrow and peripheral blood involvement, a high white blood cell count and circulating lymphocytes with highly abnormal convoluted nuclei, hypercalcemia, lytic bone lesions, cutaneous lesions often simulating those seen in mycosis fungoides, generalized lymphadenopathy, hepatosplenomegaly, interstitial pulmonary infiltrates, and central nervous system involvement in up to 25 percent of cases. The treatment is controversial, some people use combination chemotherapy others use antiviral combination of zidovudine and (-interferon but the response is usually transient.

The clinical features of ATLL in our case occurred simultaneously, not all of the manifestation appeared at the same time and the peripheral blood smear; bone marrow examination and flowcytometry were typical of ATLL. The treatment given in our case was CHOP protocol chemotherapy (Cyclophosphamid 750 mg/m, Adriamycin 50 mg/m, Vincristine 1.4 mg/m and prednisolone 100 mg orally daily for five days) with 12 mg intrathecal methotrexate, every three weeks. After four cycles she was reassessed; the skin rash had disappeared and the spleen was no longer palpable; bone marrow aspiration and biopsy suggested complete remission.

In Kyushu district, Japan, the seroprevalence HTLV-1 reaches > 30% in the adult population. In the US, Europe and the Middle East HTLV-1 infection is very rare. Cases of ATL have been reported sporadically from Iran and Israel but this the first case reported in Qatar and most likely the first in the Middle Eastern Arab countries.

**Conclusion:**

Adult T-cell leukemia/lymphoma is a rare aggressive lymphoma that may present with various clinical manifestations simultaneously. As it can be confused with other medical conditions it should form part of the differential diagnosis.


