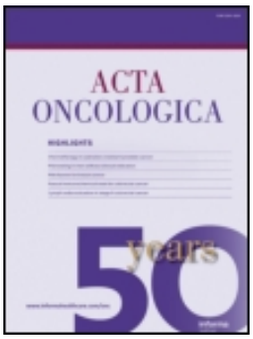

Acta Oncologica

ISSN: 0284-186X (Print) 1651-226X (Online) Journal homepage: informahealthcare.com/journals/ionc20

A suspicion of chikungunya leading to a diagnosis of angioimmunoblastic T-cell lymphoma

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To cite this article: Fadi Braiteh, Ankur Parikh & Peter McLaughlin (2009) A suspicion of chikungunya leading to a diagnosis of angioimmunoblastic T-cell lymphoma, Acta Oncologica, 48:4, 624-628, DOI: 10.1080/02841860802637773

To link to this article: https://doi.org/10.1080/02841860802637773

Published online: 08 Jul 2009.

inhibitors and has received honoraria for inclusion of patients in Pfizer-related trials. Patrick Schöffski has received honoraria for invited lectures and active participation in scientific events and advisory functions.

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A suspicion of chikungunya leading to a diagnosis of angioimmunoblastic T-cell lymphoma

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To the Editor

We report the case of a 63-year-old South-east Asian (Indian) man who presented to his family physician with fever, headache, fatigue, nausea, a pruritic macular rash on his shoulders and arms, arthralgias and myalgias. The patient and his family recently had returned from a trip to India, where the patient's 12-year-old son contracted chikungunya. The boy's symptoms—fever, headache, fatigue, nausea, vomiting, rash, myalgia, and arthralgia—resolved within a week. Because the patient's symptoms were similar to his son's, the patient thought he also may have acquired chikungunya. Chikungunya is an acute viral disease transmitted by infected mosquitoes of the genus *Aedes* and generally encountered in West Africa and South-east Asia [1]. Chikungunya generally manifests with nonspecific symptoms such as fever, fatigue, arthralgias, and a macular rash. The fever typically lasts about 2 weeks, but some patients experience prolonged fatigue that lasts several weeks. No specific antiviral treatment exists for chikungunya virus infection. The arthralgias are treated with analgesics and anti-inflammatory medication.

In the case here reported, the physical examination revealed a resolving macular rash, a tender 3-cm left axillary lymph node, without other palpable

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(Received 15 October 2008; accepted 19 November 2008)

ISSN 0284-186X print/ISSN 1651-226X online
DOI: 10.1080/02841860802637773

lymphadenopathy, and splenomegaly. Laboratory evaluation revealed microcytic anemia, eosinophilia, and elevated lactate dehydrogenase and beta-2 microglobulin levels. There was evidence of a previous cytomegalovirus infection. Serum protein electrophoresis showed two very small, relatively indistinct protein bands in the mid-gamma region. Specific serological testing for chikungunya was sent to reference laboratory and eventually the anti-chikungunya immunoglobulin M (IgM) assay came back negative. There was persistence of lymphadenopathy and the Computed Tomography (CT) scan of the patient's neck and chest showed enlarged bilateral cervical and axillary lymph nodes. Positron emission tomography (PET) revealed extensive ^{18}F-fluorodeoxyglucose (FDG) activity above and below the diaphragm, in the lymph nodes, spleen and numerous subcutaneous nodules (Figure 1, Panel A and Figure 2). An excisional biopsy of an axillary lymph node revealed peripheral T-cell lymphoma (PTCL) with features of angioimmunoblastic T-cell lymphoma (AITL). There was positive staining for CD3, CD4 (dim), and dim CD10 co-expression in some T-cells, but negative T-cell-restricted intracellular antigen-1 and Leu-7. *In situ* hybridization for Epstein-Barr virus (EBV)-encoded small RNA was negative. A bone marrow biopsy revealed atypical lymphohistiocytic aggregates with eosinophilia consistent with AITL, occupying less than 5% of the medullary space. Cytogenetic analysis showed a pseudodiploid karyotype, 6,XY,del(11)(q23),add(21q22). A fluorescence *in situ* hybridization assay ruled out chromosomal translocation t(11;21). Polymerase chain reaction analysis did not reveal any monoclonal T-cell receptor beta- or gamma-chain gene rearrangements.

Angioimmunoblastic T-cell lymphoma (AITL) is a subtype of peripheral T-cell lymphomas (PTCL). It is an aggressive lymphoma with a higher incidence in East and South-east Asia [2]. AITL commonly affects older adults, who may present with acute onset of nonspecific symptoms that include fever, fatigue, weight loss, generalized lymphadenopathy, and splenomegaly. Pleural effusion, ascites, and pruritic macular rash affect one quarter of the patients with AITL [3]. The rash is felt to result from lymphohistiocytic vasculitis. Of note, polyclonal hypergammaglobulinemia is common in patients with AITL. For the AITL, the patient was treated with a chemotherapy regimen of dose-intense cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD), to which the disease was refractory. There was only partial response after two cycles of ifosfamide, carboplatin, and etoposide (ICE). After stem cell mobilization with ifosfamide and etoposide, and conditioning with a myeloablative regimen of cytarabine, etoposide, carmustine,

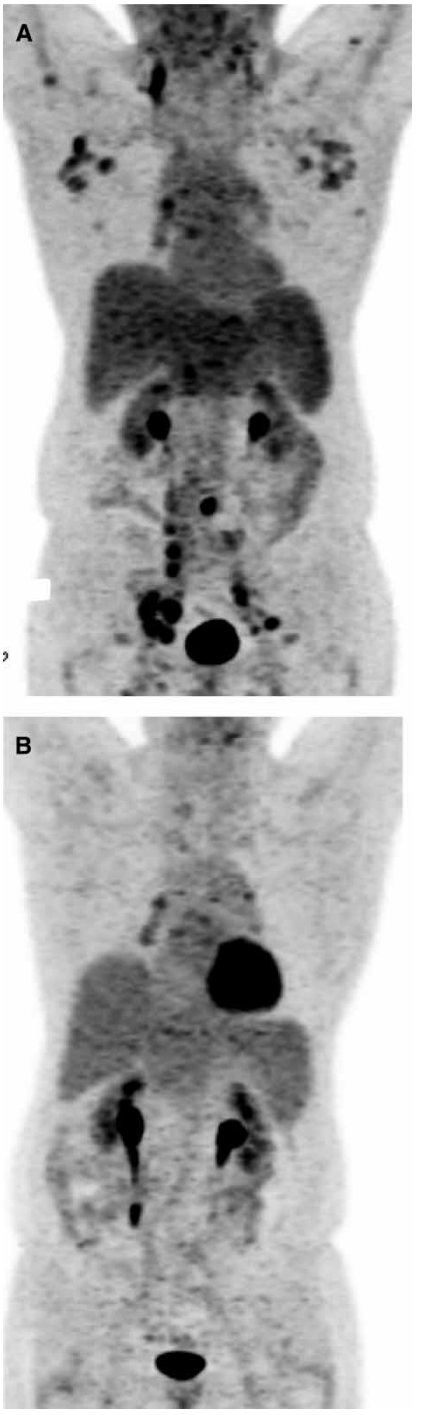

Figure 1. **A**. Initial ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) reveals mild FDG activity in bilateral jugulodigastric (standardized uptake value [SUV] of 3.5) and axillary lymph nodes (SUV of 2.7) with additional uptake noted in the right supraclavicular, right hilar, subcarinal, portocaval, mesenteric, retroperitoneal, iliac (SUV of 13.8), and inguinal lymph nodes. There is an enlargement of the spleen with increased activity (SUV of 7.1) as well. **B**. Compared to the examination obtained at diagnosis, the repeat PET scan obtained a year later shows complete remission of the disease, with no enlarged FDG-avid nodes in the neck, chest, abdomen, or the pelvis.

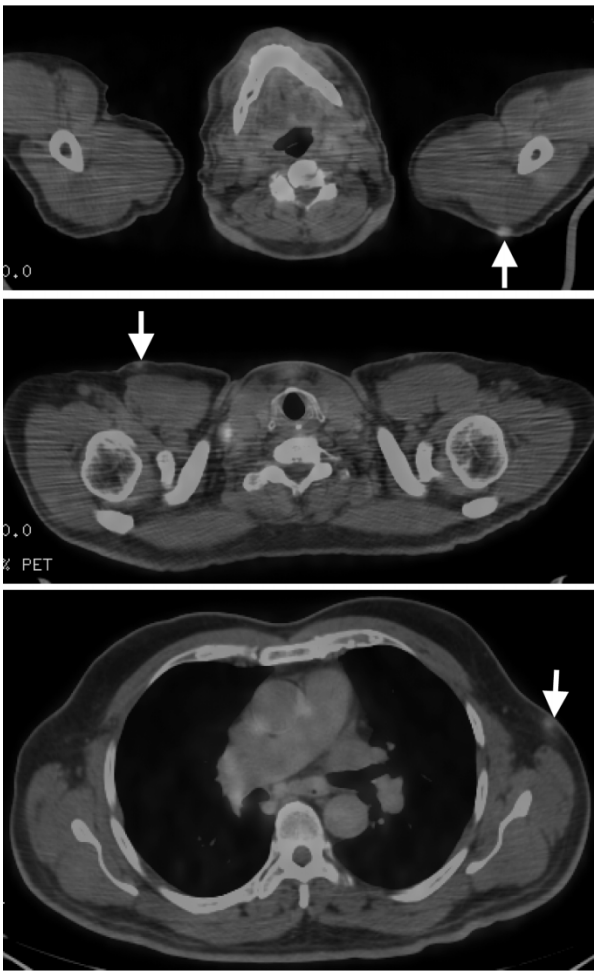

Figure 2. PET/CT scan shows numerous subcutaneous FDG-avid nodules (arrows) of cutaneous involvement by the lymphoma in the shoulder, chest wall, and axilla.

and melphalan (BEAM), the patient underwent autologous hematopoietic stem cell transplantation (HSCT). Engraftment was successful, and the patient attained complete remission for over a year after HSCT (Figure 1, Panel B). The patient ultimately had recurrent disease and did undergo an allogeneic transplant and is currently alive with no evidence of disease a month later.

In this case, the disease presentation was initially consistent with the natural history of chikungunya, but enlarged lymph nodes and constitutional symptoms prompted further investigation which revealed AITL. AITL is the second most common type of PTCL after unspecified PTCL. In the Kiel Registry, AITL accounts for 20% of T-cell lymphomas but only 4% of all lymphomas [4]. AITL is histologically characterized by polymorphous infiltration of the lymph nodes with major proliferation of endothelial venules and follicular dendritic cells. AITL has considerable histomorphologic diversity, variable immunophenotypes, and inconsistent T-cell receptor gene rearrangement. It is believed to derive from follicular helper T cells [5]. Positive flow cytometry for CD10 and the presence of EBV-encoded RNA on *in situ* hybridization are common histological features of AITL [6]. Bystander B cells including plasma cells are often present, and they probably correlate with the hypergammaglobulinemia that is commonly seen in AITL. The common expression in AITL of CXCL13, a chemokine that mediates B-cell migration, is likely related to the B-cell manifestations of AITL [7]. Roles of interleukin-6 and herpes simplex virus-8 in the etiology of AITL have been suggested but not well established [8].

The onset of symptoms of AITL may be linked with infectious diseases, antibiotic therapy, or systemic diseases such as Crohn's disease, Sjogren's syndrome, rheumatoid arthritis, drug eruption, dermatitis herpetiformis, sclerosing cholangitis, or other systemic diseases [9–11]. AITL is often detected following the administration of drugs such as sulfasalazine, salazosulfapyridine, ciprofloxacin, doxycycline, and macrolides [12,13]. The apparent association between AITL and antibiotic therapy may be coincidental, related to the empirical use of antibiotics to treat nonspecific infections when the patients' symptoms are in fact due to AITL. As reflected in the case presented, AITL's relationship with certain infectious diseases is of interest particularly in South-east Asian patients. AITL has been diagnosed at the same time as tuberculosis, hepatitis C, *Yersinia enterocolitica* infection, scabies, *Strongyloides stercoralis* hyperinfection, and endocarditis [14,15]. To our knowledge, no cases of AITL and chikungunya diagnosed concurrently have been reported. However, chikungunya has been reported to precede cases of EBV-related Burkitt's lymphoma in Africa, which suggests that populations there are exposed to multiple viruses [16].

The prognosis of AITL is poor. Traditionally, anthracycline-based chemotherapy has been used to treat AITL. Data on the management of AITL is found largely in retrospective series and case reports (Table I). Numerous treatments have some efficacy in the management of AITL, but to date there is no consensus about which regimen is best. Because of unsatisfactory results with standard therapy, numerous small studies with mixed results have explored treating AITL with alternative agents such as cyclosporine [17], fludarabine [18], cladribine [19], alemtuzumab [20], methotrexate [21], and thalidomide [22]. Some studies have shown that AITL can be effectively treated with high-dose chemotherapy followed by autologous HSCT [23]. Intensive or investigational therapy is warranted for AITL. The patient in our case had a complete

Table I. Selected published studies and reports on the treatment of AITL.

Regimen	Type of study	Number of patients	Outcome	Author (year)
High dose chemotherapy +/− Autologous HSCT	Registry review	N = 143	CR = 70%, RR + SD = 87% Median remission = 24 months OS = 59% at 4-years	Kyriakou et al. (2008) [23]
Cyclosporine	Case series	N = 12	CR = 25%, RR = 67% Duration of remission = 2–44+ months	Advani et al. (2007) [17]
High dose chemotherapy +/− Autologous HSCT	Case series	N = 19	CR = 79% OS = 60% at 2-years	Rodriguez et al. (2007) [24]
Alemtuzumab	Case report	N = 1	–	Halene et al.†† (2006) [5]
Thalidomide	Case report	N = 1	–	Dogan et al.†† (2005) [5]
High dose chemotherapy +/− Autologous HSCT	Case series	N = 29	CR = 25% OS = 44% at 5-years	Schetelig et al.†† (2003) [5]
Methotrexate +Prednisone	Case report	N = 1	–	Gerlando et al. (2001) [26]
Methotrexate +Prednisone	Case series	N = 2	–	Quintini et al. (2001) [21]
Fludarabine	Case report	N = 1	–	Bourgeois et al. (2000) [27]
Fludarabine	Case series	N = 2	–	Hast et al. (1999) [28]
Cyclophosphamide, Doxorubicin, Vincristine, Prednisone (CHOP)	Case series	N = 33	CR = 61% Median remission = 26 months OS = 65.4% at 2-years OS = 36.1% at 5-years	Pautier et al. (1999) [29]
2-CdA	Case series	N = 7	CR = 28.5%, RR = 57% Median remission = 10.5 months	Sallah et al.†† (1999) [19]
Prednisone + COPBLAM/IM VP-16†	Phase II study	N = 39	CR = 64% Median remission = 15 months OS = 34% at 3-years	Siegert et al.†† (1992) [5]
Interferon-alpha	Case series	N = 12	Median remission = 3.5 months	Siegert et al.†† (1991) [5]

† COPBLAM/IM VP-16 = cyclophosphamide, vincristine, prednisolone, bleomycin, doxorubicin, procarbazine, ifosfamide, methotrexate, and etoposide

†† Citation available in manuscript by Dunleavy et al. [10].

Abbreviations: CR = complete remission, OS = overall survival, RR = response rate.

remission for more than a year in response to autologous HSCT.

An acute onset of symptoms of fever, fatigue, arthralgias is often part of a viral syndrome. However, malignancies such as AITL should be part of the differential diagnosis, especially when body cavity effusions, atypical pruritic rash, and persistent constitutional symptoms dominate the clinical picture.

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Lack of somatic mutations in VEGFR-2 tyrosine kinase domain in hepatocellular carcinoma

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To the Editor

Hepatocellular carcinoma (HCC), is the fifth commonest malignancy and the third leading cause of cancer mortality worldwide [1]. The majority of patients present with incurable disease with dismal

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(Received 5 November 2008; accepted 20 November 2008)

ISSN 0284-186X print/ISSN 1651-226X online
DOI: 10.1080/02841860802637781