Acute Retroviral Syndrome Mimics Dengue in Singapore

Dear Editor,

Both dengue and acute human immunodeficiency virus-1 (HIV-1) can cause a febrile illness associated with myalgias, rash and blood count abnormalities, as noted in a single case report.[1] In Singapore, suspected cases of dengue are usually managed as outpatients without confirmatory testing, so acute HIV-1 may be misdiagnosed.[2] If routine confirmatory testing for dengue-like illness was performed, as recommended by the World Health Organization (WHO), misdiagnosis could be avoided. However this is difficult to implement in countries where dengue is common and patients bear the cost of testing. The objective of this retrospective study is to estimate the contribution of acute HIV-1 to dengue-like febrile illnesses through a retrospective review of hospital admission data to identify cases of probable dengue that were in fact acute HIV-1.

Materials and Methods

Cases of acute HIV-1 among inpatients were identified from the HIV service's patient register. Adults over 15 years were included if they presented between January 2010 and December 2011 with clinical features consistent with the WHO 2009 criteria for probable dengue and yet had acute HIV-1 as evidenced by a positive HIV-1 viral load and a Western blot that evolved from indeterminate to positive. Clinical and laboratory features of cases were reviewed from case notes. Emergency department databases were reviewed to find the number of patients aged over 15 years who were assigned an admission dengue diagnosis by Emergency Physicians using a pre-specified ICD-9 based coding system.

Results

A Representative Case

A 56-year-old man presented to the emergency department with 4 days of fever and rash. He had a medical history of type II diabetes mellitus, hyperlipidemia and an embolic stroke a year earlier. The patient lived in Singapore and had not travelled recently. He was afebrile at the time of initial assessment, had a blood pressure of 130/70 mmHg, heart rate of 92 beats per minute and had dry mucus membranes on physical examination. A non-pruritic blanching macular rash was present on the trunk. Diffuse abdominal tenderness was noted without guarding or rebound.

Investigations revealed a low white blood cell count of 2.83×10^9 cells/L (2.49×10^9 cells/L neutrophils, 0.22×10^9 lymphocytes) and thrombocytopenia with platelets of 78×10^9 cells/L. Aspartate transaminase (AST) was just above the normal range at 52 units/L and alanine transaminase (ALT) was 26 units/L. The patient was admitted with a clinical diagnosis of dengue. However, tests for dengue NS1 protein and viral RNA were negative.

Fourth generation HIV-1 testing performed 2 days after presentation was reactive. The Western blot evolved from indeterminate to positive over 7 weeks. Initial CD4+ T cell count was 201 cells/microliter (CD4/CD8 ratio 0.33) and HIV-1 RNA was 1.92×10^6 copies/mL. Seven weeks later, the patient's CD4+ count had increased to 359 cells/microliter (CD4/CD8 ratio 0.58) and HIV-1 RNA was 9.81×10^3 copies/mL, consistent with a final diagnosis of acute retroviral syndrome.

Case Series

Eight cases of acute HIV-1 were identified. Table 1 summarises clinical and laboratory features at presentation. Seven were admitted to hospital and met the WHO case definition for probable dengue.[3] All cases in the series were men aged 22 to 67 years. The duration of illness ranged from 3 to 8 days. Non-specific symptoms like myalgias, headache and gastrointestinal upset including nausea, vomiting or diarrhoea were common. A rash was observed in 5 cases. Five of the 8 patients had thrombocytopenia and 6 had lymphopenia.

The diagnosis of acute HIV was made using a 4th generation enzyme-linked immunosorbent assay (EIA) which detects both p24 antigen and viral antibodies and was confirmed by an evolving Western blot. During the same period, emergency physicians at our hospital assigned an admitting dengue diagnosis, using a prespecified ICD-9 based coding system, for 294 adults. The ratio of acute HIV-1 cases to those with presumed dengue was 0.024.

Conclusion

These cases illustrate how the clinical and laboratory features of acute retroviral syndrome match diagnostic criteria for probable dengue as well as the potential for misdiagnosis in dengue-endemic areas if appropriate

Table 1. Presenting clinical and laboratory features of cases of acute HIV-1

Age	Sex	Clinical presentation	Leucocytes x10⁹/L (3.40 to 9.60)	Lymphocytes x10⁹/L (0.94 to 3.08)	Platelets x10⁹/L (132 to 372)	Hematocrit (%) (37.5 to 49.3)	AST† Units/L (10 to 50)	ALT‡ Units/L (10 to 70)	HIV-1 RNA (copies/mL)	Probable dengue by WHO case classification
46	Male	Fever* for 8 days, aches & pains*, dizziness, oral ulcers, leucopenia*	2.04	0.57	106	44.1	320	322	1.34×10^6	Yes
67	Male	Fever* for 3 days, rash*, nausea/ vomiting*, aches & pains*, abdominal pain*	4.65	0.54	92	45.5	100	101	$>1.00 \times 10^7$	Yes
22	Male	Fever* for 6 days, aches & pains*, nausea/vomiting*, abdominal pain*, diarrhoea, dizziness	4.38	2.25	95	44.5	52	20	$> 1 \times 10^7$	Yes
25	Male	Fever* for 6 days, aches & pains*, nausea/vomiting*, lethargy*, headache, dehydration	4.80	0.73	145	39.1	40	71	1.57×10^5	Yes
56	Male	Fever* for 4 days, rash*, aches & pains*, abdominal pain*, dehydration, leucopenia*	2.83	0.22	78	34	26	52	1.92×10^6	Yes
43	Male	Fever* for 5 days, rash*, aches & pains*, diarrhoea, sore throat, leucopenia*	1.81	0.34	96	39.3	25	34	1.73×10^5	Yes
53	Male	Fever* for 4 days, rash*, aches & pains*, chest discomfort, dehydration	7.05	2.1	210	41.2	24	11	1.06×10^5	Yes
47	Male	Fever* for 7 days, rash*, penile ulcers	3.83	0.48	143	44.5	22	25	1.66×10^5	No

*Criteria for probable dengue (WHO 2009 case classification)

†Aspartate transaminase

‡Alanine transaminase

diagnostic tests are not performed. In addition to clinical features consistent with dengue, most of the cases had thrombocytopenia. Although thrombocytopenia is a feature of dengue, this series serves as a reminder that thrombocytopenia is not specific for its diagnosis.[4]

Conclusions about the contribution of acute HIV-1 to dengue-like febrile illness must be made cautiously, given the retrospective nature of this data. Firstly, there may be other undiagnosed cases of acute HIV-1 during the study period, thus the estimated rate may be an underestimate. A second possible concern is that hospitalised patients with probable dengue may not be representative of the majority of such patients who are managed in the community. However the clinical features and duration of illness appear consistent with typical dengue presentations. Finally, though there

may be inaccuracies in coding data, it is reasonable to conclude that acute HIV-1 is making a small but important contribution to dengue-like presentations to hospital, and in the absence of systematic testing for acute HIV-1 in the community, similar rates may exist there too.

The wide differential diagnosis for dengue is acknowledged in the WHO Dengue guidelines, and there is one published case report of acute HIV-1 mimicking dengue.[1] We have estimated the contribution of acute HIV-1 to dengue-like presentations using ICD-9 coded admission diagnoses assigned by emergency physicians as the denominator. The estimated ratio of 0.024 is concerning because not all patients with probable dengue undergo confirmatory dengue testing and fewer have HIV-1 testing. Though the overall HIV prevalence rate in Singapore remains low at

an estimated 0.1%, over half of newly-diagnosed patients continue to present with advanced disease and call our attention to the need for improved, earlier detection.[5,6] Prior HIV screening programmes have yielded HIV rates of 0.05% to 1.8% among those tested and did not focus on symptoms or early detection.[7] It is possible that the true rate of acute HIV-1 among those thought to have dengue is higher than 2.4%, suggesting this may be a population to be targeted for HIV screening.

Confirmatory testing for dengue is recommended by the WHO but utilisation of testing is low, particularly in the ambulatory care setting where the cost of dengue confirmation is difficult to justify for what is most likely a self limiting illness. Such assumptions are unfounded if the proportion of these patients with acute HIV-1 is as high as our observations suggest. Investigators have estimated the prevalence of acute HIV-1 in various clinic populations with compatible febrile syndromes. In a United States (US) hospital, 1% of those tested for acute mononucleosis had acute HIV-1, and in a Ugandan study, 1% of those presenting with malaria symptoms had acute HIV-1.[8] Corresponding data for dengue endemic areas are needed to estimate the cost efficacy of HIV testing in acute febrile syndromes.

Diagnosis of acute HIV-1 is easier with current 4th generation HIV testing which improves sensitivity and reduces the serologic window period.[8] Nucleic acid amplification testing on pooled serum has been studied as a way of diagnosing acute HIV-1 in US sexual health clinic attendees.[8] Studies on the logistics and yield of this strategy in dengue endemic settings are required to see if the promise of highly sensitive low cost testing for acute HIV-1 can be realised. There are also increasing reports on the potential benefits to patients and public health from early diagnosis and treatment of HIV-1. Furthermore, seroconversion is a period of high infectivity, so investigators hypothesise that early diagnosis, counselling and possibly treatment may reduce transmission.[8,9] Physicians in endemic areas need to consider and test for acute HIV-1 in cases of probable dengue where dengue confirmatory testing is negative.

REFERENCES

1. Cabie A, Abel S, Lafaye JM, Bera O, Cesarie R, Sobesky G. [Dengue or acute retroviral syndrome?]. Presse Med 2000;29:1173-4.

2. Lee LK, Thein LT, Kurukularatne C, Gan VCH, Lye DC, Leo YS. Dengue knowledge, attitudes, and practices among primary care physicians in Singapore. Ann Acad Med Singapore 2011;40:533-8.

3. Special Programme for Research and Training in Tropical Diseases, World Health Organization. Dengue : guidelines for diagnosis, treatment, prevention, and control. New ed. 2009, Geneva: TDR : World Health Organization, 2009.

4. Chadwick D, Arch B, Wilder-Smith A, Paton N. Distinguishing dengue fever from other infections on the basis of simple clinical and laboratory features: application of logistic regression analysis. J Clin Virol 2006;35:147-53.

5. Ministry of Health (2011) Update on the HIV/AIDS situation in Singapore 2011. Available at: http://www.moh.gov.sg/content/dam/moh_web/PressRoom/Articles/2012/Annex_HIV%20Figures%202011.pdf. Accessed 31 July 2012.

6. World Health Organization and the Joint United Nations Programme on HIV and AIDS (UNAIDS) (2009) Epidemiological fact sheet on HIV and AIDS 2009: Singapore. Available at: http://www.unaids.org/en/regionscountries/countries/singapore/. Accessed 31 July 2012.

7. Chua AC, Leo YS, Cavailler P, Chu C, Ng A, Ng OT, Krishnan P. Opt-out of voluntary HIV testing: a Singapore hospital's experience. PLoS One 2012;7:e34663. Epub 2012 Apr 6.

8. Pilcher CD, Christopoulos KA, Golden M. Public health rationale for rapid nucleic acid or p24 antigen tests for HIV. J Infect Dis 2010;201:S7-15.

9. Cohen MS, Shaw GM, McMichael AJ, Haynes BF. Acute HIV-1 Infection. N Engl J Med 2011;364:1943-54.

Ayesha Verrall, [1]*MBChB, MBHL, DTMH*, Jun Hao Tan, [2],
Sophia Archuleta, [1]*MD*

[1]Division of Infectious Diseases, University Medicine Cluster, National University of Singapore
[2]Yong Loo Lin School of Medicine, National University of Singapore

Address for Correspondence: Dr Sophia Archuleta, Division of Infectious Diseases, University Medicine Cluster, National University Hospital, 1E Kent Ridge Road, NUHS Tower Block, Level 10, Singapore, 119228.
Email: sophia@nus.edu.sg