Supplemental Information

DESCRIPTION OF THE EBV PCR USED

DNA was extracted from 200 μL of whole blood with a QIAamp DNA blood mini kit. Epstein Barr DNA was amplified with an in-house real-time polymerase chain reaction (PCR) method targeting the *EBNA-1* gene. The sequences of the forward primer, the reverse primer, and the probe were 5′-GAC TGT GTG CAG CTT TGA CGA T-3′, 5′-CAG CCC CTT CCA CCA TAG GT-3′, and 5′ CCT CCC TGG TTT ML -3′, respectively. The probe was labeled at the 5′ end with 6-carboxyfluorescein (FAM) and at the 3′ end with Minor Groove Binder (MGB) (Applera, Courtaboeuf, France). The threshold value of the PCR test was 500 copies/mL.

METHODS

This systematic review was carried out in accordance with Centre for Reviews and Dissemination guidelines for systematic reviews.[1]

DATA SOURCE

We carried out a thorough search of Medline and Isi Web of Knowledge databases, from their inception to January 2010, for all clinical reports (case reports, case series, cohort studies, trials) of children presenting multicentric Castleman disease. The search strategy was based on the use of medical subject heading (MeSH) terms and free text words, including the following: "child," "infant," "children," "preschool child," "adolescent," "Castleman disease," and "giant lymph node hyperplasia." The electronic search was enhanced by hand-searching of the reference lists of all the articles identified, and all appropriate articles identified in this manner were subsequently obtained. The electronic search was validated by comparing the list obtained with the reference lists of previous reviews on Castleman disease (mono- or multicentric form, adults, children, or both together)[2–5] to identify any systematic defects that might be present. No language restriction was used. One reviewer (SL) screened the titles and abstracts from the electronic searches against the inclusion and exclusion criteria and considered for inclusion reports of children with multicentric Castleman disease. If insufficient information was available to make a decision, the full article was read and, in some cases, discussed with a second reviewer (SP) until a consensus was reached.

STUDY ELIGIBILITY

We included all reports meeting the following criteria: children with multicentric Castleman disease. Children were considered to be under 18 years of age, and multicentric Castleman disease was defined on the basis of typical histological findings (hyaline vascular type, plasma cell type, or mixed type) in patients presenting disease at more than 1 site (including nodal involvement and hepatosplenomegaly), with constitutional symptoms and/or immune and hematologic abnormalities.[5] Duplicate reports were excluded, and the analysis was restricted to pediatric patients. No limitations relating to study design were applied.

DATA EXTRACTION

One reviewer (SL) abstracted the data from each study to obtain information about the year of publication, the type of study, the number of patients reported, their geographic origin if known, their age, gender, disease presentation and course, treatment, histologic findings, testing for viral infection if any, and any other relevant information relating to the patient. The reviewer (SL) extracted the data and completed a standardized electronic spreadsheet. All uncertainties were discussed with a second reviewer (SP) until a consensus was reached. Where necessary, the authors were contacted to obtain additional data or to clarify the information presented.

ANALYSIS

We described the studies included, the characteristics of the children presenting multicentric Castleman disease, and the histological and viral characteristics of the various cases reported. Statistical analyses were carried out with Stata/SE 10 software (StataCorp, College Station, TX).

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SUPPLEMENTAL TABLE 2 Systematic Review of Clinical Reports of Pediatric Patients with Multicentric Castleman Disease and No Immunodeficiency

Article	Author Location	Patient Origin[a]	Gender	Age	Clinical Features	Hist	HHV-8 Expl
Lee, 1965[1]	New York (NY)	Italian	M	8	Mediastinal LA and mass, SM, growth retardation, fever, anemia (6 g/dL), biological inflammatory syndrome, plasmacytosis on bone marrow aspiration.	PC	NR
Carring-ton, 1989[2]	Man-chester (UK)	NR	M	16	Supraclavicular, axillary LA, HSM, AIHA, thrombocytopenia and neutropenia. Recurrence of thrombocytopenia 17 mo later: CT, Danazol, VC were effective, but the patient remained neutropenic.	MT	NR
Said, 1992[3]	Amman (Jordan)	NR	M	14	Fever, asthenia, generalized LA, HSM, anemia, membranoproliferative glomerulonephritis type 1 leading to a nephrotic state. Treatment with CT.	PC	NR
O'Reilly, 1993[4]	Green-ville (NC)	AA	F	12	Fever, mediastinal LA and mass, HSM, anemia, thrombocytopenia, mild hepatic dysfunction, renal insufficiency due to glomerulonephritis. Low IL-6 levels. Death from respiratory distress due to the increased mediastinal mass.	MT	NR
Kinney, 1994[5]	Nashville (TN)	AA	M	2	Fever, inflammatory SD, generalized LA, SM, generalized papular rash, glomerulonephritis (hematuria, pyuria, renal failure), polyarthritis, AIHA, unexplained cerebrovascular stroke (leading to seizure). High IL6 levels in blood and on lymph node biopsy. Treatment with CT, AZA.	PC	NR
Taylor, 1994[6]	Ronde-bosch (South Africa)	Eastern Cape, Ciskei region of South Africa	M	3	Cervical and hilar LA, HSM, AIHA. Association with KS lesions.	PC	NR
			M	8	Generalized LA, HSM, fever, low IgA levels	PC	NR
			M	6	Cervical and abdominal LA, SM, inflammatory SD. Association with B-cell gastric lymphoma.	PC	NR
			M	5	Generalized LA, HSM, fever	PC	NR
			F	11	Generalized LA, inflammatory SD. Association with KS lesions.	PC	NR
Vergin, 1995[7]	Izmir (Turkey)	NR	M	13	WT syndrome. Three cervical masses, mediastinal LA, HSM, severe AIHA (2 g/dL), high IgG levels. Effective treatment with CT, IgIV.	HV	NR
Smir, 1996[8]	Omaha (NE)	One of African origin, 1 Hispanic, 6 European	F	2	Rash, generalized LA, HM, repeated infections, growth retardation, anemia, impaired liver function. Treatment with CT, IgIV, MTX.	PC	NR
			F	3	Pneumonia, generalized LA, fever, anemia, thrombocytopenia. Treatment with CT, IFN.	PC	NR
			F	6	Rash, generalized LA, HM, edema, ascites, effusion AIHA, thrombocytopenia, impaired liver and renal function. Treatment with CT.	HV	PCR HHV-8- on biopsy[c]
			F	10	Rash, edema, generalized LA, underweight, HM, AIHA. Treatment with CT.	HV	NR
			F	12	Mediastinal mass, ascites, effusion, generalized LA, HM, anemia, thrombocytopenia, GN (proteinuria), impaired liver and renal function. Death shortly after surgery.	PC	PCR HHV-8- on biopsy[c]
			M	15	Axillary and cervical LA, HM, gingivitis, sinusitis, AIHA, thrombocytopenia, neutropenia. Treatment with IgIV.	PC	PCR HHV-8- on biopsy[c]
			F	16	Retroperitoneal LA, arthralgia, cutaneous nodules, hydronephrosis, edema, anemia, thrombocytopenia. Treatment with CT and by splenectomy.	PC	PCR HHV-8- on biopsy[c]
			M	17	Rash, edema, ascites, generalized LA, HM, AIHA, thrombocytopenia, MPGN (proteinuria, hematuria), impaired renal and liver function. Treatment with CT and by plasmapheresis.	HV	NR

SUPPLEMENTAL TABLE 2 Continued

Article	Author Location	Patient Origin[a]	Gender	Age	Clinical Features	Hist	HHV-8 Expl
Arslan, 1996[9]	Kayseri (Turkey)	NR	M	8	Rash, mesenteric and mediastinal LA, HSM, bilateral uveitis, hepatitis, nephrotic syndrome (proteinuria), biological inflammatory syndrome, seizures (normal cerebral CT-scan). Course with multiples relapses.	HV	NR
Nakamura, 1997[10]	Shiga (Japan)	NR	M	12	Generalized peripheral LA, mediastinal LA, interstitial pneumonia, anemia, thrombocytopenia, proteinuria, high blood IgG and IL-6 levels. Effective treatment with CT and immunosuppressive drugs.	PC	NR
Akyuz, 2000[11]	Ankara (Turkey)	NR	F	10	Bilateral cervical masses then generalized LA, HSM benign course for 3 y then T-cell lymphoma (stage IV). Death after respiratory distress during lymphoma treatment, after 5 y of MCD.	NR[b]	NR
Kosucu, 2003[12]	Trabzon (Turkey)	NR	M	5	Wt loss, growth retardation, axillary, supraclavicular LA, multiple subpectoral masses, HSM. Treatment by surgery and radiation therapy.	HV	NR
Baserga, 2005[13]	Orange (CA, US)	Hispanic origin	F	4	Fever, generalized LA, HM, diarrhea, vomiting, ascites and hypertension related to renal failure (dialysis), anemia, thrombocytopenia. Treatment with chemotherapy (CT,DX, VC, CyP), and IgIV. Free of disease 36 mo after treatment.	MT	HHV-8 – on biopsy[d]/blood[d]
Zakiullah, 2006[14]	Karachi (Pakistan)	NR	M	16	Abdominal pain, malaise, wt loss, cervical and abdominal LA, hepatic mass, HSM, anemia. Courses of chemotherapy (CT, CyP).	HV	NR
Robinson, 2006[15]	Melbourne (Australia)	NR	F	18	Inguinal, axillary and mediastinal LA (few clinical details available)	PC	NR
Vasudev Rao, 2007[16]	Muscat (Oman)	Oman	M	18	Fever, loss of wt and appetite. Generalized LA, thoracoabdominal LA, HSM, weakness of both legs due to cerebral lesions. Anemia, biological inflammatory syndrome (high IL6 level). Treatment with multiple courses of chemotherapy, achieving remission. Then AIHA treated with CT. Free of disease since treatment.	MT	NR
Sharma, 2007[17]	New Delhi (India)	NR	M	6	Fever, generalized LA, mesenteric and mediastinal LA, HM, bilateral pleura effusion, anemia, biological inflammatory syndrome, high IgG level, biological hepatitis. Treatment with CT, free of disease (44 mo of FU).	HV	NR
		NR	M	7	Cervical, axillary and mesenteric LA, discrete generalized LA, HSM, anemia, thrombocytopenia. Treatment with multiple courses of CT, with a transient effect on thrombopenia, then with 5 CHOP cycles, achieving remission.	MT	NR
Lee, 2008[18]	Seoul (South Korea)	NR	F	14	Multicentric Castleman disease.	HV	HHV-8- on biopsy[e]
Galeotti, 2008[19]	Bicetre (France)	Hispanic origin	M	6.5	Fever, chills, polyarthralgia. Then multiple episodes of unexplained fever, HSM, mesenteric and retroperitoneal LA, infiltrative mass located between the pancreas and splenic hilum. Six courses of chemotherapy (CyP, VB, rituximab) then IL-1RA agonist, CT and colchicine resulting in persistent remission.	MT	HHV-8 serologyf
Sobrevilla-Calvo, 2009[20]	Mexico City (Mexico)	NR	M	15	Cervical and retroperitoneal LA. Benign course after 1 CHOP cycle.	HV	NR

AA, African American; AIHA, autoimmune hemolytic anemia; AZA, azathioprine; CHOP, combined chemotherapy with prednisone, vincristine, cyclophosphamide and doxorubicin; CyP, cyclophosphamide; CT, corticosteroids; DX, doxorubicin; Expl, exporations; F, female; FU, follow-up; GN, glomerulonephritis; HHV-8, human herpes virus 8; HIST, histology; HM, hepatomegaly; HSM, hepatosplenomegaly; HV, hyaline vascular type; IFN, interferon; Ig, immunoglobulin; IgIV, intravenous immunoglobulin; IL, interleukin; KS, Kaposi sarcoma; LA, lymphadenopthy; M, male; MPGN, membranoproliferative glomerulonephritis; MT, mixed type; MTX, methotrexate; NR, not reported; PC, plasma-cell type; SM, splenomegaly; VB, vinblastine; VC, vincristine; WT syndrome, autosomal dominant condition, combining hematologic abnormalities (anemia, pancytopenia, leukemia, lymphoma) with mild limb defects (ulnar and radial defects, bifid or hypoplastic thumbs and cutaneous syndactyly).

[a] Consanguinity was explicitly investigated (questioning of parents and other tests) and reported. In such cases, this finding is also indicated in the clinical features cell.

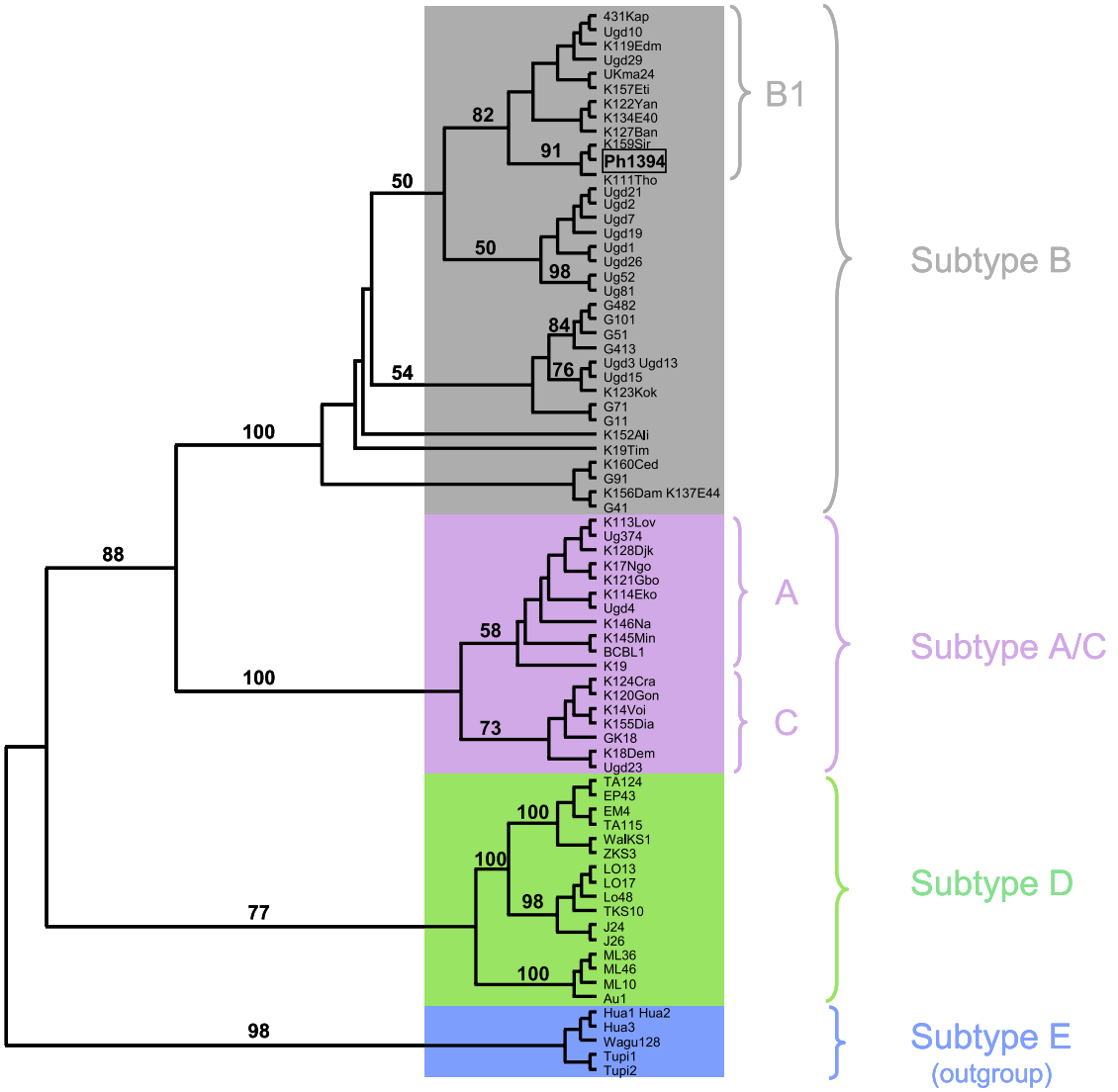
[b] The histologic pattern of the lymph node was typical of giant node hyperplasia, but the histologic type was not specified.

[c] PCR analysis to detect the presence of HHV-8 in biopsy specimens.

[d] HHV-8 serology (no other details given), testing for HHV-8 based on the immunoperoxidase staining of paraffin-embedded biopsy tissue.

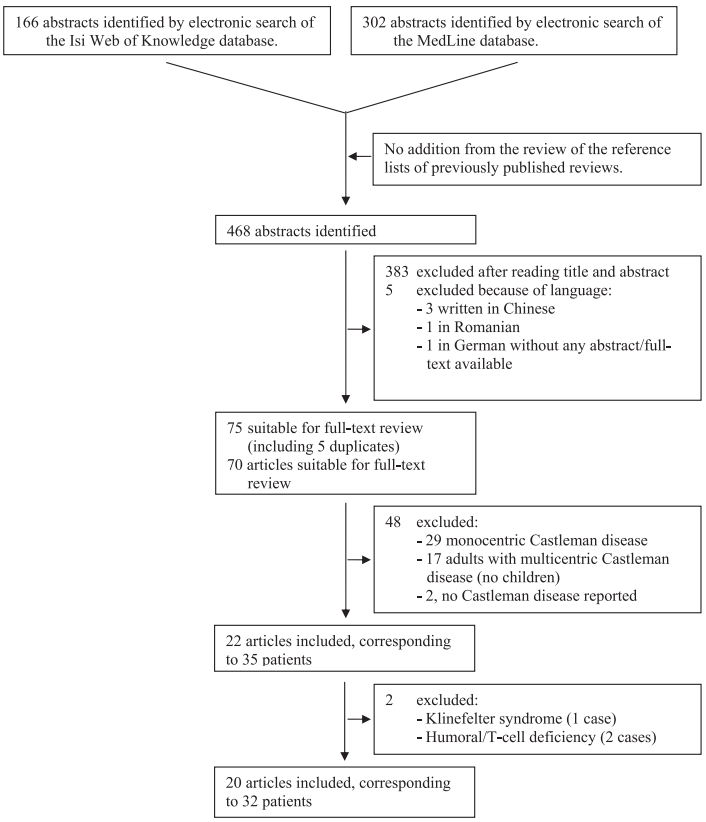
[e] Immunohistochemical study carried out on biopsy specimens with antibodies directed against HHV-8 LANA.

[f] No details provided concerning the technique used for HHV-8 serology.



SUPPLEMENTAL FIGURE 2

Phylogenetic tree constructed by the neighbor-joining method in PAUP (v4.0b10), based on a 624-bp fragment of the K1 ORF for the 77 available human herpes virus 8 (HHV-8) sequences, including the sequence generated in this work (in bold type). The DAMBE program (version 4.2.13) was used to align the HHV-8 sequences. The final alignment was input into the Model test program (version 3.6) to select the best model, according to the Akaike information criterion for phylogenetic analyses. The selected model was the Kimura 3-parameter model. Bootstrap values were calculated for 1000 replicates and the numbers at some nodes of the tree (bootstrap values) indicate frequencies of occurrence for 100 trees. A through E correspond to the 5 HHV-8 subtypes and B1 to a group within the sub-Saharan African B subtype, described by the following references in the main text of this article: Lacoste et al 2000,[8] White et al 2008,[9] and Kajumbula et al 2006.[10]



SUPPLEMENTAL FIGURE 3
Flowchart for the systematic literature review