Figure 1 Vitamin B supplements purchased over the counter at a health food store. Each capsule contains 100 mg of pyridoxine, which is 50 times the recommended daily intake.

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Exacerbation of chronic active Epstein–Barr virus infection in a patient with rheumatoid arthritis receiving humanised anti-interleukin-6 receptor monoclonal antibody

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We describe deterioration of chronic active Epstein–Barr virus (CAEBV) infection in a patient with rheumatoid arthritis who received a single infusion of humanised anti-IL6 receptor monoclonal antibody (tocilizumab). A 60-year-old woman with rheumatoid arthritis who had been treated with methotrexate developed lymphadenopathy in October 1999, which was ameliorated in 2 months by cessation of methotrexate. Re-institution of methotrexate in September 2000 led to recurrence of lymphadenopathy, which was diagnosed as necrotising lymphadenitis by histological examination, with high titres of anti-Epstein–Barr virus (EBV) antibodies (antiviral capsid antigens IgG 1:1280, anti-early antigens IgG 1:640) and EBV DNA in plasma (3100 copies/ml). The lymphadenopathy gradually disappeared after cessation of methotrexate at the expense of active arthritis. In July 2001, the patient was enrolled in a clinical trial for tocilizumab¹ and intravenously treated with the trial drug (8 mg/kg). Arthritis dramatically improved, but EBV DNA increased from 520 (3 September 2001) to 2600 copies/10⁶ white cells (12 September) and liver enzymes also increased. The patient became febrile and showed hepatosplenomegaly, pleural effusion and

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blepharoeedema. She was diagnosed as having haemophagocytic syndrome and capillary leak syndrome with exacerbation of CAEBV infection^{2–3} according to her clinical manifestations and laboratory data including results of bone marrow biopsy. Treatment with high-dose corticosteroid, cyclosporin A and IL-2 activated T cells⁴ was not effective. Multiple gastric ulcers were identified by gastrointestinal fibroscope. She died of disseminated intravascular coagulation and multiple organ failure (fig 1).

Because of this tragic complication, the amounts of EBV DNA in other patients enrolled in the same clinical trial were measured, but this was the only patient who showed EBV DNA of over 2000 copies/10⁶ white cells. Considering the fact that IL-6 regulates growth, differentiation and activation of cytotoxic T lymphocytes,^{5–8} it is plausible that blockade of IL6–IL6 receptor interaction by tocilizumab would have resulted in the final breakdown of immunosurveillance for EBV. The treatment with tocilizumab might have exacerbated

Abbreviations: CAEBV, chronic active Epstein–Barr virus; EBV, Epstein–Barr virus

Figure 1 Clinical course of the patient.

Figure 2 Histopathological features of the lymph node (A), liver (B) and bone marrow (C,D) at autopsy. (A) Small blue-black dots in the nuclei indicate EB-encoded small RNA (EBER)-1 mRNA by in situ hybridisation in Hodgkin's lymphoma cells (arrows; original magnification ×50). (B) Thin arrows indicate CD45RO+ T cells by immunohistochemistry. Thick arrow indicates both EBER-1-positive (in situ hybridisation) and CD45RO+ T cells (original magnification ×400). (C) Brown staining indicates CD68+ cells (original magnification ×50). (D) Histiocytes with haemophagocytosis were observed (arrows; haematoxylin and eosin staining; original magnification ×200).

pre-existing Hodgkin's disease (see below) and worsened the clinical course. The present case strongly indicates that treatment with tocilizumab should be avoided for patients with underlying CAEBV infection. The amount of EBV DNA in white cells should be measured before the institution of tocilizumab when patients show clinical manifestations suggestive of CAEBV infection.

Autopsy showed enlarged para-aortic and mesenteric lymph nodes. Histologically, small islands of lymphocytes were seen in lymph nodes, with scattered large atypical lymphocytes which were positive for CD15 and CD30 but negative for CD3, CD4, CD20, CD56 and CD68. These characteristics are compatible with Hodgkin's lymphoma cells (Reed–Sternberg cells) and these lymphocytes expressed EB-encoded small RNA-1 (EBER-1) (fig 2A). Infiltrating CD45RO+ T lymphocytes in the liver were also EBER-1+ (fig 2B). The bone marrow was mainly occupied by CD68+ histiocytes with haemophagocytosis (fig 2C, D). The stomach had multiple ulcerations owing to infiltration of both Hodgkin's lymphoma cells and EBER-1+ lymphocytes. A small number of Hodgkin's cells were retrospectively identified in the biopsy specimen of the lymph node at the recurrence of lymphadenopathy in March 2001.

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Evaluation of cardiac functional abnormalities in systemic sclerosis by dobutamine stress echocardiography: a myocardial echostress scleroderma pattern

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In this study, we investigate the possibility of detecting, by dobutamine stress echocardiography (DSE), the presence of early or subclinical myocardial functional changes in patients with systemic sclerosis (SSc) without symptoms of ischaemic cardiac involvement.

Thirty consecutive patients with SSc (26 women and four men; mean age 51 years, range 28–73 years), with a mean disease duration of 8 years (range 1–21 years), were studied. In all, 16 of 30 patients with SSc were affected by diffuse cutaneous (dc)-SSc, and the remaining 14 patients had limited cutaneous (lc)-SSc. The study was approved by the local ethics committee, and all patients gave informed consent to participate. All patients fulfilled the American College of Rheumatology preliminary classification criteria for SSc.¹ Table 1 lists the demographic and clinical data of patients with SSc. Four patients with dc-SSc (25%) and two with lc-SSc (14%) had hypertension, and three patients with dc-SSc (19%) had diabetes; all were well controlled by appropriate treatment.

The DSE protocol was applied as follows: after baseline data were acquired, dobutamine was infused, beginning at a dose of 5 µg/kg/min and increasing every 3 min to a maximum dose of 40 µg/kg/min. Echocardiograms were recorded at baseline, low dose, peak dose and 5 min into recovery. When necessary, atropine (up to 1 mg) was given intravenously at higher dose to augment the heart rate response (fig 1). The duration of the whole examination was 30 min.

The electrocardiogram and blood pressure were monitored continuously and recorded at each stage. For segmental analysis of left ventricular function, a 16-segment model was

used, as suggested by the American Society of Echocardiography.²

In 13/30 (43%) patients with systemic sclerosis, a wall motion abnormality, which was absent on baseline rest examination, was observed during dobutamine infusion. These changes were observed in 9/16 (56%) patients with dc-SSc and in 4/14 (28%) patients with lc-SSc, showing a higher frequency in the diffuse cutaneous subset. Owing to the small size of the two patient subsets, this difference did not reach significance ($p = 0.17$).

Table 1 Demographic and clinical features of patients with systemic sclerosis

	dc-SSc		lc-SSc	
	Data	Range	Data	Range
Demographic and clinical features				
Number of patients	16		14	
Mean (SD) age (years)	53 (13.1)	28–71	52 (9.3)	39–73
M/F ratio	1/14		3/12	
Mean (SD) disease duration (years)	8 (3.3)	2–15	8.5 (5.8)	1–21
Clinical manifestation (n (%))				
Raynaud phenomenon	16 (100)		12 (85)	
Teleangiectasias	12 (75)		5 (36)	
Lung involvement	13 (81)		4 (29)	
Oesophageal involvement	14 (88)		1 (7)	
Trophic ulcers	10 (62)		6 (43)	
Calcinosis	0		5 (36)	

dc-SSc, diffuse cutaneous systemic sclerosis; F, female; lc-SSc, limited cutaneous systemic sclerosis; M, male.