Polyarthritis following interferon alpha treatment in a patient with localized Wegener's granulomatosis

Sirs,

Localized Wegener's granulomatosis (WG) was diagnosed in a 40-year-old women with subglottic stenosis and biopsy-proven necrotizing granulomatous vasculitis in November 1987. cANCA was 1:256 with specificity for proteinase-3. Cotrimoxazole therapy (1) led to complete remission. The patient was found to be in remission on interdisciplinary stagings (2) over the next 10 years. cANCA (tested every 3 months) remained positive (1:128 - 1:512).

In December 1998 increased liver enzymes were observed: GOT 191 U/l, GPT 437 U/l, GGT 85 U/l, AP 253 U/l. The patient felt well. There were no signs of WG activity, but the cANCA titer had risen (1:1024) (Table I). Further investigations revealed an HCV infection. Previously collected frozen serum samples were assayed and HCV-RNA was detected in a probe from October 1998, but no HCV-antibodies. The mode of transmission remained unclear. A liver biopsy disclosed acute hepatitis with incipient portal fibrosis. Rheumatoid factor, cryoglobulins, HIV, hepatitis B, antinuclear antibodies, antimitochondral antibodies were negative, but a rise in activated T-cells was discernible by FACS. Treatment with interferon- 2b 3 x 5 Mio. IU/week s.c. plus ribavirin 2 x 600 mg/day induced the elimination of HCV-RNA in the serum with low-level HCV antibodies found in April 1999. Liver values were normalized. The cANCA titer did not change. Antiviral therapy was continued.

In June 1999 the patient complained of a symmetrical polyarthritis for the first time. Cryoglobulins and rheumatoid factor remained negative. Joint scintigraphy revealed enhancement over multiple small and large joints. The cANCA titer had increased to 1:4096, and activated T-cells became discernible again. Serum HCV-RNA remained undetectable. The HCV-antibody level was low, and liver tests were normal. Antiviral therapy was stopped. The arthritis necessitated treatment with methotrexate (20 mg/week) plus prednisone (7.5 mg/day). During the following weeks, the polyarthritis resolved and signs of inflammation in the blood normalized. HCV-RNA remained undetectable. WG was in remission. However, the cANCA titer did not change.

Three hypotheses may explain the polyarthritis in this case:

(i) *Polyarthritis and HCV infection.* Rheumatic complaints are frequently observed in chronic HCV infection (23% - 35%) (3-5). However, arthritis is rare (< 5%) (5). In our case HCV-RNA was undetectable with low-level HCV-antibodies at the time of the occurrence of polyarthritis. An increase in T-cell receptor- expression was observed to values comparable with an acute HCV infection (6). Thus, HCV infection could have become active again after temporary normalization of values during antiviral treatment and despite the failure to demonstrate HCV-RNA serologically at this time.

(ii) *Interferon- and polyarthritis.* Interferons may have multiple effects on the immune system,and may induce or exacerbate autoimmune diseases, including polyarthritis (7). In most cases, discontinuation of interferon led to improvement of the arthritis. The incidence of arthritis under interferon is low (<1% - 2%) (7-9). The mean elapsed time from the initiation of interferon to the onset of arthritis was 8 months (7); in our case it was 6 months. Pre-existing autoantibodies may be a risk factor for autoimmune diseases occurring with interferon- therapy (10). However, there is no information on the pre-existence of ANCA, e.g. PR-3 ANCA, and the risk of autoimmune disease with interferon- .

(iii) *Transformation from localized to generalized WG caused by interferon-* This hypothesis is supported by an increase of activated T-cells (11) in conjunction with a rising ANCA titer (12) at the time the polyarthritis arose. There have been reports of an exacerbation of vasculitis under interferon- treatment, e.g. in HCV-associated cryoglobulinemic vasculitis (13-15). Although there were no signs of WG activity in other organ systems, we have seen patients in whom polyarthritis was the first clinical sign of WG.

In conclusion, we report a patient with localized WG in remission. Polyarthritis was seen while a newly diagnosed HCV infection was being treated with interferon- plus ribavirin. The polyarthritis occurred when HCV-RNA was no longer detectable. Thus, an association of polyarthritis with interferon- therapy was more likely than an association with HCV infection. However, interferon- may have triggered a transformation from localized to generalized WG. Patients with pre-existing autoimmune diseases, in whom interferon- therapy has been started, require close surveillance for the occurrence of side effects of interferon and for exacerbation of the pre-existing autoimmune disease.

Table I. Clinical,serological-immunological course of a patient with longstanding localized WG since 1987 plus acute hepatitis C infestion 10/98.

	5/97	10/98	12/98	4/99	8/99	11/99
cANCA titer	1: 64	1: 256	1: 1,024	1: 1,024	1: 4,096	1: 2,048
ESR (mm/1 hr)	2	10	10	10	20	8
C-reactive protein (mg/dl)	< 0.5	< 0.5	< 0.5	< 0.5	1.8	< 0.5
White blood cell count	4.300	6.100	5.300	5.300	4.800	6.900
Platelets (x 10^3)	284	303	300	350	396	309
Clinical symptoms *	-	-	-	B	A, B	-
Therapy **	T/S	T/S	T/S	IF + Ribavirin	IF + Ribavirin	MTX + Prd
HCV AB (extinction)	0	0	57	24	7	3
HCV RNA (copies/ml)	0	1 x 10^5	9 x 10^3	< 10^2	< 10^2	< 10^2
Activate T lymphocytes (HLADR/CD3) #	4%	5.8%	11%	ó%	11%	7%
T cell receptor ##	NI	85%	86%	92%	87%	94%
T cell receptor ###	NI	13%	12%	7%	11%	5%

*A:rheumatic complaints (in this case, polyarthritis); B:constitutional symptoms; **T/S:trimethoprim/sulfamethoxazole; MTX:methotrexate; Prd:prednisone. #Normal value:2% ± 2; ##Normal value:94% ± 1. ###Normal value:4% ± 1%; NI: no information.

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The historical record is consistent with the recent finding of parvovirus B19 infection of bone marrow in systemic sclerosis patients

Sirs,

Recently Ferri *et al*. have found parvovirus B19 (PVB19) DNA in bone marrow biopsies of 57% of 21 systemic sclerosis (SSc, scleroderma) patients, but 0% of 15 controls (1). This is consistent with their interesting idea (2) that PVB19 may play a role in the etiology of SSc. As Ferri *et al.* note, it is important for other groups to be able to replicate this finding. Until then, and as well, complementary with positive replications, I here point out that the historical record is currently consistent with a role for PVB19 in the pathogenesis of SSc.

The first report of SSc was not until 1753 by Curzio (3) [and even this case has been disputed (4)], and there is a possible case of SS in a 1680 painting (5). Thus, it appears that SSc is a relatively new disease. The absence of evidence is not evidence of absence, of course; in times past there were far fewer patients,physicians, and researchers, and SSc is not a trivial diagnosis. Nevertheless, the relatively late description of this disease is in the very least intriguing. If, in fact, SSc is a new disease, this suggests that at least one of the proposed etiologic agents of SSc (most likely a disease requiring multiple elements to be present for pathogenesis, e.g. genetic + environmental) must also be new. Interestingly, it appears that PVB19 is.

There was no PCR and no Centers for Disease Control in centuries past to track the appearance of a virus but, as I have recently noted (6), the pediatric exanthem erythema infectiosum (EI, "fifth disease"), which is characterized by a "slapped cheek" rash and high infectivity and is now known to be caused by PVB19 (7), can be used to track the antiquity of PVB19. EI, and thus PVB19, appear to be "new" – the first report of a disease consistent with EI did not appear until 1797 (7, 8).

How can a ubiquitous virus such as PVB19 be "new ?" Much work, not without dispute (see ref. 9 and refs. therein), has found that PVB19 may play a role in the pathogenesis of rheumatoid arthritis (RA). From examination of writings, paintings, and the work of Rothschild and colleagues on skeletons (ref. 10 and refs. therein),it appears that RA is quite a new disease in Europe (less than 500 years old), but it has existed in North America for thousands of years. Recently, I have suggested (6) that PVB19 was brought back from the New World to the Old. This time frame for the introduction of PVB19 to Europe (after 1500) is consistent with the current historical record for SSc (and PVB-19).

Besides EI, PVB19 is known to cause aplastic anemia, hydrops fetalis, and fulminant liver failure (11) – more than enough reasons to spur on the development and possible implementation of a PVB19 vaccine. If such a vaccine were put into use, it would help clarify the role of PVB19 in RA and SSc, much as the measles vaccine did for the role of measles in subacute sclerosing panencephalitis. Conversely, further evidence that PVB19 plays an etiologic role in SSc and/or RA would provide increased impetus for vaccine development.

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