Pleuritis is a red flag for adult-onset Still's disease which may require biologic therapies

Sirs,

Adult-onset Still's disease (AOSD) is a rare systemic inflammatory disorder of unknown aetiology and pathogenesis (1-2), characterised by heterogeneous clinical manifestations (1-3). Biologic agents appeared effective in severe and refractory cases (4), however, their implementation may be convenient earlier in such cases.

In order to explore the clinical and/or laboratory findings at onset of AOSD that could lead to use biologic treatments to disease control, we focused on the clinical and laboratory presentation of 36 patients [25 males and 11 females, median age 36 years (range 16–75)] with diagnosis of AOSD (5), who were all the AOSD patients referring to our Clinic from 2003 to 2011, *i.e.* since biologics have been available.

All patients received glucocorticoids (34/36, 94.4%) or NSAIDs (14/36, 38.9%) or both (12/36, 33.3%) at disease onset. Methotrexate was used in 31/36 (86.1%), other DMARDs alone or in combination with methotrexate in 22/36 (61.1%).

Biologic agents were used in 12/36 cases (33.3%) with serious and/or refractory AOSD. Anakinra was used in 10 patients, etanercept in 8 cases, infliximab and adalimumab in 4 patients respectively, tocilizumab in 2 cases, and abatacept and certolizumab in one patient, respectively. Biologic treatments were finally effective in controlling the disease in all but one patient who died due to uncontrolled disseminated intravascular coagulation, diagnosed late, and, notably, before the institution of the biologic agent.

Globally, the median (25 to 75 percentiles) time of exposure to biologic therapies was 22 months (12.75–42.75). Seventeen switches from one to another biologic therapy occurred in 7/12 patients (58.3%), and they occurred 9 times for inefficacy or loss of response [etanercept (3), infliximab (2), adalimumab (1), anakinra (1), certolizumab (1), tocilizumab (1)], while 8 times for side effects [mild thrombocytopenia with anakinra (n=2), diverticulitis or new onset of demyelinating-like syndrome with etanercept (n=2); urticarial rash with anakinra (n=3), or with etanercept (n=2)].

At the last follow-up, a biologic treatment was still used in 8 patients (anakinra in 3/8, adalimumab in 2/8, etanercept, adalimumab and tocilizumab in 1 patient, respectively), while in the remaining 3 patients one DMARDs was using as maintenance therapy (azathioprine or chloroquine or cyclosporine A). Low doses of glucocorticoids were continued in 3 patients.

Table I. Frequencies of the features observed in patients needing or not needing biologic therapies.

Features	Total (n=36)	Biologic therapy (n=12)	No Biologic therapy (n=24)	*p*-value*
Fever	36/36	12/12	24/24	NA
Sore throat	23/36	7/12	16/24	0.7
Cutaneous rash	22/36	7/12	15/24	1.0
Arthritis/arthralgias	33/36	12/12	21/24	0.5
Pleuritis	10/36	7/12	3/24	0.007
Pericarditis	11/36	5/12	6/24	0.4
Lymphoadenopathy	21/36	7/12	14/24	1.0
Splenomegaly	8/36	3/12	5/24	1.0
Leucocytosis (WBC >10000/mmc)	31/36	11/12	20/24	0.6
Elevated liver enzymes	12/36	4/12	8/24	1.0

*statistics were computed by Fisher's exact test for categorical variables. NA, not applicable.

Among the following manifestations at onset, fever, leukocytosis, arthritis or arthralgias, cutaneous rash, sore throat, hepatitis, splenomegaly, lymphoadenopathy, pericarditis, pleuritis, only pleuritis was significantly associated with the use of biologics (7/12 *vs*. 3/24 (19.2%); p=0.007, OR 9.8, 95% CI 1.8–51.9) (Table I).

Interestingly, pleuritis was associated with a slightly higher number of therapies employed [median (range): 3, (1-8) *vs*. 2, (1-10); p=0.04, Mann-Whitney test)] during the course of the disease (data not shown).

AOSD is a rare inflammatory disease that currently remains a clinical challenge despite novel effective treatments (6, 7). Multi-organ involvement may compromise the outcome and thus requires an aggressive diagnostic work-up and therapeutic strategy. Treatment of AOSD is difficult also because of the heterogeneity of the clinical manifestations and for the absence of treatment guidelines.

In our study, biologic therapies were more often required in those patients with AOSD presenting with pleuritis. Pleuritis may then identify AOSD with higher or persistent disease activity, which may require biologic therapies in the follow-up. Pleuritis has been already recognised as unfavourable prognostic factor for patients with AOSD (8), and it has been associated with higher serum macrophage migration inhibitory factor levels that were closely correlated with disease severity and activity (9). Also, pleuritis is a clinical manifestation of severe active disease in other settings, *e.g.* systemic lupus erythematosus or autoinflammatory diseases (10). Thus, pleuritis may represent a clinical red flag for clinicians involved in the management of AOSD.

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