

Scientific Letter

Visceral serositis in acute Epstein-Barr virus infectious mononucleosis: systematic review of the literature

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Acute symptomatic Epstein-Barr virus infectious mononucleosis (mononucleosis) is a benign disease that presents with sore throat, swollen lymph nodes or splenomegaly and resolves over ≤ 8 weeks [1]. In a minority of cases, however, a wide range of complications occur [2]. Pericardial serositis has been reported in cases with myocarditis, peritoneal serositis in cases with pancreatitis, cholecystitis or appendicitis, and pleural serositis in cases with pneumonia [2].

Otherwise unexplained pericardial, peritoneal or pleural serositis are further uncommon complications of mononucleosis. To integrate existing information, we conducted a systematic review in the National Library and Excerpta Medica databases. We selected reports published after 1959, which describe previously healthy individuals affected by either symptomatic or atypical mononucleosis and an otherwise unexplained visceral or peritesticular serositis.

The diagnosis of symptomatic mononucleosis [1] was made in cases with fever and at least one of three findings (sore throat, swollen cervical lymph nodes or splenomegaly) and a positive serology for acute disease. Results of tests for Epstein-Barr virus detection were also considered. Absolute and atypical lymphocytosis were defined as recommended [3].

The diagnosis of atypical mononucleosis was made in subjects with a positive serology but without sore throat, swollen cervical lymph nodes or splenomegaly and absent blood smear abnormalities [3]. The diagnosis of otherwise unexplained serositis was made in cases with pericardial serositis and normal myocardial function, in cases with ascites unassociated with appendicitis, cholecystitis or pancreatitis, or in cases with pleural serositis without associated pneumonia. The effusion to blood total protein or lactate dehydrogenase gradient was used to support the diagnosis of exudative effusion.

The diagnosis of possible peritesticular serositis was made in cases with mononucleosis associated with testicular swelling and tenderness.

Cases with increased proteinuria or with a pre-existing condition possibly explaining the development of visceral serositis were excluded.

Liver enzyme levels were used to diagnose hepatocellular, cholestatic or mixed liver damage [3]. Hematologic complications such as thrombocytopenia and hemolytic anemia are common in mononucleosis. Following definitions were used: thrombocytopenia if platelet count $\leq 150 \times 10^9/l$, leukopenia if total white cell count $\leq 4.5 \times 10^9/l$ and hemolytic anemia if anemia was associated with at least one of the following

findings: increase in reticulocyte count (or nucleated red blood cells in peripheral blood smear), positive direct Coombs test or decreased haptoglobin level [3]. Finally, the diagnosis of post-infectious fatigue was made in patients without any physical finding more, who reported debilitating fatigue and disabling cognitive or musculoskeletal symptoms not relieved by rest, which persisted for ≥ 3 months. Results are given as frequency or as median and interquartile range, as appropriate. The rank-sum test for independent samples was used to compare continuous and the Fisher exact test to compare categorical variables.

The initial literature search returned 950 articles (including 126 duplicates). Upon completion of screening, the full text of 131 articles was assessed. For the final analysis, we retained 27* articles reporting 28 cases published between 1960 and 2018: 12 from Europe, 12 from North America and 3 from Asia. Following laboratory data supported the diagnosis of infectious mononucleosis in the 28 cases: Paul-Bunnell-Davidsohn test (N=15), IgG against the early Epstein-Barr viral antigen (N=15), or IgM against the Epstein-Barr viral capsid antigen (N=13). In two cases, the Epstein-Barr virus was also detected in blood.

Twenty-one reports described 22 patients aged from 1.2 to 80 years of age with mononucleosis and a pericardial, a peritoneal or a pleural serositis (figure 1). Infectious mononucleosis was symptomatic in 18 (82%) and atypical in 4 (18%) cases. The characteristics of the 22 patients appear in table 1. Patients with atypical mononucleosis were older ($P < 0.02$) than those with symptomatic mononucleosis. Furthermore, a pericardial effusion, either isolated or combined, was found in all 4 cases with atypical mononucleosis and in no more than 5 of the 18 cases with symptomatic mononucleosis ($P < 0.02$). A cardiac tamponade requiring drainage was observed in 6 out of 9 cases. A peritoneal or a pleural drainage was performed in 6 and 5 cases, respectively. Laboratory testing, performed in peritoneal (N=4), pleural (N=3) or pericardial (N=2) fluid, always confirmed the clinical diagnosis of exudative effusion. Testing for Epstein-Barr virus detection, performed in 4 pericardial and 3 pleural effusions, was positive. Fever, sore throat, lymphadenopathy, splenomegaly and the serosal effusions resolved within 3 to 26, median 6 weeks. The findings persisted for ≥ 10 weeks in only 2 cases. Post-infectious fatigue occurred in 2 cases.

The remaining reports described six subjects aged from 4.0 to 29 (median 16) years affected by symptomatic mononucleosis with testicular

swelling and tenderness (right, N=3; left, N=2, bilateral, N=1). Imaging studies of the scrotum were not performed. An association with a pericardial, a peritoneal or a pleural effusion was never reported. Blood smear abnormalities were reported in 5 out of the 6 cases. Furthermore, a hepatocellular liver damage was reported in 3 of them. Testicular swelling and tenderness fully resolved within 1 to 11, median 7 weeks.

This review suggests that the association between mononucleosis and otherwise unexplained visceral serositis is very uncommon but plausible and occasionally life-threatening. In previously healthy subjects, cytomegalovirus and herpes simplex virus type 2 have also been anecdotally associated with a visceral serositis. The current analysis included also 6 subjects with symptomatic mononucleosis and testicular swelling and tenderness. Since none of the cases presented also with a pericardial, peritoneal or pleural inflammation, we wonder if testicular swelling and tenderness was due to orchitis or to an inflammation of the peritesticular serosa [4].

In conclusion, diagnosis and management of mononucleosis are generally straightforward [1]. This study points out that this condition can occasionally be a major challenge [1, 2]. It is true, however, that the vast majority of patients with lymphadenopathy and serositis suffer from noninfectious diseases such as malignancy or inflammatory conditions including among others systemic lupus erythematosus or Still's disease [5].

* The list of the 27 reports describing original cases of infectious mononucleosis complicated by serositis is available on request (email: milani.gregoriop@gmail.com)

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Figure 1 - legend

Venn diagram depicting pericardial, peritoneal or pleural serositis in 22 patients affected with either symptomatic (N=18) or atypical (N=4) Epstein-Barr virus infectious mononucleosis.

Table 1: Clinical and laboratory findings in 22 patients (ranging in age from 1.2 to 80 years) with primary acute Epstein-Barr virus infection complicated by an otherwise unexplained visceral serositis. Results are given either as frequency or as median and interquartile range (which includes half of the data).

Epstein-Barr Virus Infectious Mononucleosis			
	All	Sympto- matic	Atypical
N	22	18	4
Male : Female, N	13/9	10/8	3/1
Age, years	19 [15-33]	18 [14-23]	49* [34-60]
Blood smear abnormalities	15	15	0*
Visceral serositis			
Monovisceral, N	10	8	2
Pericardial, N	4	2	2
Peritoneal, N	3	3	0
Pleural, N	3	3	0
Multivisceral, N	12	10	2
Pericardial and peritoneal, N	0	0	0
Pericardial and pleural, N	3	2	1
Peritoneal and pleural, N	7	7	0
Peritoneal, pleural and pericardial, N	2	1	1

Liver damage, N	13	11	2
Hepatocellular, N	7	6	1
Cholestatic, N	2	2	0
Mixed, N	2	2	0
Unclassified, N	2	1	1
Hematologic complications, N	7	6	1
Thrombocytopenia, N	5	5	0
Leukopenia, N	1	0	1
Hemolytic anemia, N	1	1	0
Post-infectious fatigue, N	2	2	0

‡ Inclusion criterium, *P<0.05 versus symptomatic cases, patient with isolated pericarditis and mild pre-existing alcoholic liver disease without portal hypertension.

Visceral Serositis in Epstein-Barr Infectious Mononucleosis

Peritoneal

Pleural

Pericardial

Figure 1