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Acute kidney injury in symptomatic primary Epstein-Barr virus infectious mononucleosis: Systematic review

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ABSTRACT

Background and objectives: Textbooks and reviews do not mention the association of symptomatic primary Epstein-Barr virus infectious mononucleosis with acute kidney injury in subjects without immunodeficiency or autoimmunity.
Study design: Stimulated by our experience with two cases, we performed a review of the literature.
Results: The literature documents 38 cases (26 male and 12 female individuals ranging in age from 0.3 to 51, median 18 years) of symptomatic primary Epstein-Barr virus infectious mononucleosis complicated by acute kidney injury: 27 acute interstitial nephritides, 1 jaundice-associated nephropathy, 7 myositides and 3 hemolytic uremic syndromes. Acute kidney injury requiring renal replacement therapy was observed in 18 (47%) cases. Acute kidney injury did not resolve in one patient with acute interstitial nephritis. Two patients died because of systemic complications. The remaining 35 cases fully recovered.
Conclusions: In individuals with acute symptomatic Epstein-Barr virus infectious mononucleosis, a relevant kidney injury is rare but the outcome potentially fatal. It results from interstitial nephritis, myositis-associated acute kidney injury, hemolytic uremic syndrome or jaundice-associated nephropathy.

1. Background and objectives

In subjects without immunodeficiency or autoimmunity [1], symptomatic primary Epstein-Barr virus infectious mononucleosis, subsequently simply referred to as infectious mononucleosis, is the distinctive acute manifestation of Epstein-Barr virus [1]. It typically affects children and young adults, presents with fatigue, poor appetite, fever, sore throat, enlarged cervical lymph nodes, liver or spleen, and lymphocytosis composed in large measure of atypical lymphocytes. The condition typically uneventfully resolves over a period of weeks [1].

In symptomatic primary infectious mononucleosis, altered urinalysis has a reported frequency of between 5% and 15% [2]. Nonetheless, textbooks and reviews do not mention its possible association with acute kidney injury [3], with the exception of occasional cases of myositis-associated kidney injury [2].

Over the past years, we made the diagnosis of acute kidney injury in two patients with symptomatic infectious mononucleosis [4,5]. Stimulated by these observations, we conducted a review of the literature.

2. Study design

2.1. Literature search strategy

Between February and September 2016, we performed a search with no date limits of the Medical Subject Headings terms (Drüsenfieber OR Epstein-Barr virus OR glandular fever OR Herpesvirus 4 OR infectious mononucleosis OR kissing disease OR Pfeiffer's disease) AND (acute kidney injury OR acute renal failure OR hemolytic-uremic syndrome OR interstitial nephritis OR rhab-

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domyolysis) in the US National Library of Medicine and Excerpta Medica databases. Personal files and the bibliography of each identified report were also screened. We applied the principles established by the Economic and Social Research Council guidance on the conduct of narrative synthesis and on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. The literature search was performed independently by two investigators (MM, MGB). Conflicts were resolved by consensus.

2.2. Selection criteria

For the final analysis, we selected reports published as full-length articles or letters, which describe previously healthy individuals without personal history of immunodeficiency or autoimmunity concurrently affected with symptomatic infectious mononucleosis and acute intrinsic kidney injury.

The diagnosis of (a) infectious mononucleosis, (b) acute interstitial nephritis, (c) myositis-associated acute kidney injury or (d) hemolytic-uremic syndrome established in the original publications was reassessed using prospectively defined criteria. (a) The diagnosis of symptomatic primary infectious mononucleosis [2] was made in cases with negative past history for infectious mononucleosis, at least four of eight symptoms or findings (eyelid edema, fatigue and poor appetite, fever, hepatomegaly, jaundice, sore throat, splenomegaly, swollen cervical lymph nodes) and a positive serology (positive Paul-Bunnell-Davidsohn heterophile antibody test, IgM antibodies against the Epstein-Barr viral capsid antigen or IgG antibodies against the early Epstein-Barr viral antigen). The possible occurrence of absolute ($\geq 6.0 \times 10^9$/L in subjects $\leq$13 years of age; $\geq 4.0 \times 10^9$/L in older subjects) and atypical (large lymphoid cells $\geq$10% of total lymphocytes) lymphocytosis was also addressed [6]. Cases with a positive serology but without clinical features were excluded. (b) The diagnosis of acute interstitial nephritis [7] was made in cases with urinalysis disclosing white cells (with or without cell casts), a negative urine culture for bacteria, non-nephrotic range proteinuria and acute kidney injury. A renal biopsy disclosing a marked interstitial infiltrate consisting primarily of mononuclear inflammatory cells with normal glomeruli and blood vessels was not a prerequisite for the diagnosis. The possible association of interstitial nephritis with uveitis was also explored [8]. Cases of interstitial nephritis possibly induced by drugs [9] and cases with chronic onset were not included. (c) The diagnosis of myositis-associated acute kidney injury [10] was made in cases with creatine kinase $\geq$30 times the upper reference limit, positive urine orthotoluidine-dipstick test for "blood" in the absence of red cells on microscopic examination, and acute kidney injury. Cases of "myositis" possibly caused by potentially myotoxic drugs or triggered by intense, repetitive exercise or a sudden increase in exercise in an untrained person $\leq$3 days before myositis onset were excluded. (d) The diagnosis of acute hemolytic-uremic syndrome [11] was made in cases with hemolytic anemia, microscopic evidence of red blood cell fragmentation, platelet count $\leq 150 \times 10^9$/L, and acute kidney injury. Hemolytic-uremic syndrome cases likely caused by a shigatoxin-producing microorganism or by a pneumococcus were excluded.

Patients infected simultaneously with Epstein-Barr virus and a second pathogen, with reactivation of Epstein-Barr virus infection, with chronic active Epstein-Barr virus infection, with acute kidney damage not associated with altered kidney function, with a pre-existing chronic kidney disease and with chronic onset of kidney disease were excluded. Circulating creatinine was used to define acute kidney injury as absolute increase in circulating creatinine by $\geq$27 μmol/L above the upper limit of normal for age and gender or an increase by at least 1.5 times baseline [3]. Kidney injury was classified [3] as stage I (increase in creatinine by 1.5–1.9 times baseline, or increase by $\geq$27 μmol/L above the upper limit of normal for age), stage II (increase in creatinine by 2.0–2.9 times baseline) and stage III (increase in creatinine by $\geq$3.0 times baseline, or increase in creatinine by $\geq$354 μmol/L, or the initiation of renal replacement therapy).

We exclusively retained original cases of both sexes and all ages irrespectively of follow-up duration. Reports published in languages other than Dutch, English, French, German, Italian, Portuguese or Spanish were excluded.

Table 1
Symptoms, findings, serology and laboratory characteristics of symptomatic primary Epstein-Barr virus infectious mononucleosis reported in 38 cases (26 male and 12 female subjects ranging in age from 0.3 to 51, median 18 years) complicated by acute kidney injury.

	N	%
Symptoms and findings		
Eyelid edema	6	16
Fatigue and poor appetite	38	100
Fever	38	100
Hepatomegaly	19	50
Jaundice	13	34
Sore throat	32	84
Splenomegaly	19	50
Swollen cervical lymph nodes	32	84
Blood smear abnormalities		
Absolute lymphocytosis	18	47
Atypical lymphocytosis	19	50
Microbiological studies		
Positive heterophile antibody test[a]	29[a]	76
IgM against Epstein-Barr viral capsid antigen	34	89
IgG against early Epstein-Barr viral antigen	9	24
Epstein-Barr virus polymerase chain reaction	2	5

[a] The serological diagnosis was made on the basis of this test alone in 3 cases published before 1980.

2.3. Data extraction and analysis

From each report dealing with symptomatic primary Epstein-Barr virus infection and acute kidney injury, data on gender; age; clinical, laboratory and histological findings; non renal complications (e.g. thrombocytopenia); management and clinical course were excerpted using a structured schedule established in advance. Data were extracted independently by two investigators. Discrepancies were solved by consulting a senior researcher.

Results are given either as frequency or as median and interquartile range, as appropriate. The Cohen's kappa index was used to assess the agreement between investigators on the application of the inclusion and exclusion criteria.

3. Results

3.1. Search results

Thirty-two peer-reviewed scientific reports (Fig. 1) published between 1955 and 2015 in English (N = 28), German (N = 2), Italian (N = 1) and Spanish (N = 1) were retained for the final analysis [4,5,12–41]. The chance-adjusted agreement between the two investigators on the application of the inclusion and exclusion criteria was 0.87.

The retained articles were reported from the United States of America (N = 14), Switzerland (N = 3), Canada (N = 2), Israel (N = 2), the United Kingdom (N = 2), Finland (N = 1), Germany (N = 1), Italy (N = 1), Japan (N = 1), Peru (N = 1), South Korea (N = 1), Taiwan (N = 1), The Netherlands (N = 1) and Turkey (N = 1). They included 38 cases of symptomatic primary infectious mononucleosis (Table 1) complicated by acute kidney injury: 27 acute interstitial nephritides, 1 jaundice-associated nephropathy, 7 myositides and 3