

Human parvovirus B19 infection mimicking systemic lupus erythematosus in an adult patient

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We report a case of widespread immune activation with moderate cytopenia during acute infection with human parvovirus B19 in an adult female patient, in whom five criteria for the diagnosis of systemic lupus erythematosus were present at disease onset. Our case is unusual due to the presence of a cutaneous rash mimicking leukocytoclastic vasculitis at presentation, moderate leukopenia with thrombocytopenia and the presence of a broad array of autoantibodies. Diagnosis was established on the grounds of serological tests confirming recent infection with human parvovirus B19; spontaneous regression of clinical and laboratory abnormalities was observed within 16 weeks, ruling out classic systemic lupus erythematosus. We conclude by proposing that human parvovirus B19 infection should be included in the differential diagnosis of lupus-like syndromes in adult patients.

(Ann Ital Med Int 2001; 16: 125-127)

Key words: Autoantibodies; Parvovirus; Systemic lupus erythematosus.

Introduction

Human parvovirus B19 (HPV-B19) is a small single-stranded DNA virus that is host-specific and requires dividing host cells for its replication. Infection by this virus produces classical erythema infectiosum (fifth disease) in children; moreover, it is associated with a variety of clinical syndromes, including intrauterine embryopathy, aplastic crisis in patients with chronic hemolytic anemia, acute or chronic arthropathy, purpuric vasculitis, hypocomplementemia, thrombocytopenia and leukopenia mediated by bone marrow suppression, most of which can also be observed in systemic lupus erythematosus (SLE). Furthermore, HPV-B19 infection can be associated with rheumatoid factor (RF), antinuclear (ANA), anti-double-stranded DNA (anti-ds-DNA) and anti-cardiolipin (ACA) antibodies¹⁻⁵.

In addition, it has been reported that HPV-B19 infection may induce or exacerbate SLE^{1,6,7}, and some case reports have documented that it may mimic SLE in both adult and pediatric populations^{5,8,9}.

We report a case of acute HPV-B19 infection in an adult patient who met at least five criteria for the diagnosis of SLE at presentation.

Case report

A 29-year-old previously healthy woman was admitted to our hospital because of a 2-week history of arthralgia, sore throat, myalgia and fatigue without fever. A few days after symptom appearance, a mild pruritic macu-

lopapular rash developed on her abdomen, which then extended to her arms and legs. Two weeks earlier, her son had had typical erythema infectiosum. The patient's history was otherwise unremarkable. She did not report previous clinical signs of arthritis or unexplained fever; she also denied any recent drug use, as well as known food or drug allergy. Her family history did not disclose any immune or allergic diseases.

At presentation, the patient was afebrile and had a rash suggesting leukocytoclastic vasculitis on her trunk, upper arms and legs; she also had mild swelling of the wrists, metacarpophalangeal and proximal interphalangeal joints. The lymph nodes were not palpable, and there were no other abnormal findings on physical examination. An abdominal ultrasound scan evidenced only mild splenomegaly.

Laboratory analysis showed leukopenia (white blood cells 1.69×10^3 cells/mm³), thrombocytopenia (platelet counts 102×10^3 cells/mm³) and mild nonhemolytic anemia (hemoglobin 11 g/dL) with a negative Coombs' test and low reticulocyte count. Her erythrocyte sedimentation rate was 47 mm/h. There were no abnormal findings on urinalysis; renal and liver function tests were normal. Serological and immunological tests were as follows: ANA were positive (titer 1:40, speckled pattern); anti-ds-DNA and RF were also positive (1:20 and 90 IU/mL, respectively); anti-SSA/Ro and anti-SSB/La antibodies were negative; ACA immunoglobulin (Ig) M were elevated (39.6 MPL-U/mL). As for complement levels, only C3 was low (56 mg/dL), while C4 was 24 mg/dL (normal range C3 88-201 mg/dL; C4 16-47 mg/dL). Anti-platelet antibodies were negative. Microbiological and serological tests did not disclose signs of bacterial infection or acute hepatitis B virus, *Cytomegalovirus* or *Toxoplasma gondii*

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infection, while serology for HPV-B19 was positive for both IgM and IgG (16; positivity > 1.2). A cutaneous biopsy showed no signs of vasculitis, and immunofluorescence tested negative for C3 and Ig deposition. A bone marrow biopsy was not performed.

One week later, the rash and other symptoms resolved completely without any medical treatment. The leukocyte and platelet counts returned to normal levels; C3 and erythrocyte sedimentation rate level were also normal. Three weeks later, ANA and anti-ds-DNA were still positive at titers of 1:40 and 1:10, respectively. IgM and IgG (36) for HPV-B19 were also weakly positive. Six weeks later, the patient was completely asymptomatic, the leukocyte and platelet counts were normal, but the C3 level was still low (63 mg/dL); ANA and anti-ds-DNA were unchanged (1:40 and 1:20, respectively). RF was also positive (75 U/mL, normal values 0-20 U/mL), as well as IgM and IgG (16) for HPV-B19. Ten weeks later, the leukocyte and platelet counts were normal, C3 level was low (63 mg/dL), ANA (1:40), anti-ds-DNA (1:20), RF (103 U/mL), IgM and IgG (7.5) for HPV-B19 were weakly positive. Sixteen weeks later, the leukocyte and platelet counts were normal and the other laboratory and immunological abnormalities were no longer detectable.

Discussion

We report a case of HPV-B19 infection in an adult patient with clinical, hematologic and serological abnormalities mimicking those frequently observed in SLE. The diagnosis of HPV-B19 infection was based upon the positivity of specific anti-HPV-B19 IgM antibodies. At disease onset, the patient fulfilled at least five American College of Rheumatology criteria for the diagnosis of SLE, according to the revision proposed by Hochberg¹⁰. However, before HPV infection, there had been no clinical or laboratory findings suggestive of SLE, and subsequently clinical and immunologic abnormalities resolved within 16 weeks without therapy. Thus, the symptoms in our patient were clearly related to HPV-B19 infection and were not a manifestation of SLE.

In 1992, Kalish et al.¹¹ reported two cases of "lupus-like" presentation during acute HPV-B19 infection. In 1993, Chassagne et al.¹² described exacerbation of SLE during HPV-B19 infection, and Cope et al.¹³ described a case of HPV-B19 infection coincident with SLE onset. Subsequently, some case reports of adult and, rarely, pediatric patients with HPV-B19 infection simulating SLE have been published: as reviewed by Neshet et al.⁵, there were striking analogies in clinical and laboratory signs between HPV infection and SLE. At presentation, our patient met five American College of Rheumatology criteria for the diagnosis of SLE; accordingly, most of the previously described cases fulfilled three to five of the above-mentioned criteria. Nevertheless, Neshet et al.⁵ proposed

that several findings may help distinguish between the two conditions, inasmuch as patients with HPV-B19 infection do not develop discoid lesions, alopecia or Raynaud's phenomenon, and fever is usually absent or of short duration. Moreover, neurologic, cardiac and renal involvement is rare. Our patient had no hematuria or proteinuria, nor did she show signs of serositis, cardiomyopathy or neurological involvement. However, a prominent feature in this case was the co-existence of a cutaneous rash, suggestive of vasculitis, with arthritis, cytopenia and immunologic abnormalities. This presentation pointed to SLE in the initial differential diagnosis. In fact, HPV-B19 infection can trigger an autoimmune response, with a higher incidence in females, and the production of various autoantibodies, e.g. ANA, anti-ds-DNA, anti-SSA or anti-SSB, antiphospholipid antibodies and RF. Also, similarities have been recently described in the specificity of antiphospholipid antibodies of patients with HPV-B19 infection and those of patients with SLE¹⁴. Lunardi et al.¹⁵ in 1998 proposed that some regions of the capsid protein VP2 of HPV-B19 may mimic autoantigens, and they reported that the antibodies against these regions are found particularly in more severe HPV-B19 infection.

Compared with the cases reported to date, our patient had relatively mild elevation of autoantibody titers; however, in none of the previously described cases was such a wide array of autoantibodies detected. On the other hand, in line with other case reports, in our patient, autoantibodies were present at disease onset and resolved within several weeks without therapy. In most of the previously described cases, autoantibodies disappeared within 3 to 12 months, although Vigeant et al.¹⁶ reported the case of a patient with prolonged detection of ANA and anti-Ro antibodies.

Clinical evidence of symmetric small joint arthritis was observed in our patient at presentation. Arthropathy associated with HPV-B19 infection is the rule in the cases reported to date in the literature. Although its distribution may mimic that of rheumatoid arthritis, it is, as occurred in our case, usually transient and non-destructive. Its pathogenesis is unknown, even though both an immune complex mechanism and persistent infection have been hypothesized¹⁰. Either normal^{5,6} or low^{1,10,11,15} C3/C4 levels have been previously reported in the presence of clinical signs of arthritis. In view of the persistently depressed C3 values found in our case, the presence of circulating immune complexes cannot be ruled out. However, immune complex mechanisms did not seem to be massively activated, inasmuch as there was neither evidence of glomerulopathy, nor were clear histological signs of vasculitis seen on skin biopsy, nor C3 and Ig deposits detected at immunofluorescence.

Parvovirus infection is common, and about 50% of adults may have antibodies against this virus¹; nevertheless, only a minority of patients develop clinically impor-

tant disease. In 1996, Hemauer et al.¹⁷ described that HPV-B19 originating from infections with rarely-occurring or severe symptoms displays an elevated nucleotide variability when compared to HPV-B19 virus from patients with erythema infectiosum. However, the same authors have recently reported a low level of mutations in B19 viral genome from a patient who had SLE and was simultaneously infected by this virus, suggesting an individual genetic predisposition rather than a viral cause for the development of more severe disease⁷. Although specific HLA haplotypes may seem appealing candidates, no increased association of chronic HPV-B19-induced arthropathy with HLA-DR4 (as in classical rheumatoid arthritis) has been demonstrated¹⁸.

In summary, our report and others demonstrate that infection with HPV-B19 can present with clinical and laboratory manifestations that are highly suggestive of SLE. Therefore, careful search for a history of previous contacts with patients with erythema infectiosum is very important. Moreover, since IgM antibodies against HPV-B19 disappear within 8-10 weeks in the majority of patients¹, the diagnosis may be missed if serological testing for this virus is not performed soon after the onset of symptoms.

In conclusion, we suggest that acute HPV-B19 infection be included in the differential diagnosis and that appropriate serological tests be carried out during the evaluation of patients with a first episode of lupus-like syndrome; spontaneous clinical remission may help clarify the diagnosis.

Riassunto

Gli autori descrivono un caso di infezione acuta da parvovirus B19 in una giovane donna, in cui erano riscontrabili cinque criteri per la diagnosi di lupus eritematoso sistemico all'esordio. Le caratteristiche cliniche di rilevante interesse erano rappresentate da rash cutaneo suggestivo per vasculite leucocitoclastica, leucopenia e trombocitopenia moderate e riscontro di ampia attivazione autoanticorpale. La diagnosi veniva formulata sulla base di test sierologici indicativi di infezione recente da parvovirus B19. Il quadro clinico e laboratoristico si risolveva spontaneamente nel corso di 16 settimane, consentendo di escludere il lupus eritematoso sistemico. Gli autori suggeriscono di includere l'infezione da parvovirus B19 nella diagnosi differenziale delle sindromi "lupus-like" nell'adulto.

Parole chiave: Autoanticorpi; Parvovirus; Lupus eritematoso sistemico.

Manuscript received on 16.10.2000, accepted on 23.1.2001.

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