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Human Parvovirus B19 and polymyalgia rheumatica: a case report and short review of the literature

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ABSTRACT:

Acute B19 virus infection is classically associated with a widespread benign and self-limiting childhood rash illness, known as erythema infectiosum (EI) or fifth disease. The clinical presentation associated with B19 infection may vary greatly, ranging from benign forms of arthralgias to life-threatening conditions, depending on age and immunologic status. A case of polymyalgia rheumatica (PMR) in a 74-years-old woman affected by B19 virus infection is reported here, presenting with evening low-grade fever, shoulder and pelvic girdle arthralgia and functional impairment. A comprehensive review of the literature showed that B19 virus has been hypothetically implicated as the causative or precipitating agent of several autoimmune and rheumatic diseases, including PMR. Some molecular mechanisms underlying the autoimmune phenomena have been described, involving the inflammatory response due to cytokine activation, the formation and deposition of immune complexes and molecular mimicry mechanisms. Nowadays, the reports in the literature, which have focused on the possible role of Parvovirus B19 in the pathogenesis of PMR, are few and discordant. Therefore, further and more in deep investigations are needed, hopefully leading to a final consensus between researchers.

Keywords: Parvovirus B19, Viral Infections, Autoimmunity, Rheumatology.

INTRODUCTION

Human Parvovirus B19 is a very small, non-enveloped, single-stranded DNA virus, which belongs to the Erythrovirus genus within the Parvoviridae family, being the predominant member of this family pathogen in humans (genotype 1)[1]. Other rather rare and only recently described Erythroviruses infecting humans include genotype 2, typical of western countries (e.g., Europe and The United States) and genotype 3, dominant in sub-Saharan Africa and South America[2,3]. Human Parvovirus PARV4 and human Bocavirus (HBoV) are also newly discovered human Parvoviruses which epidemiology and disease association are still poorly understood[4].

B19 virus was discovered in 1974[5] while evaluating tests for hepatitis B virus surface antigen. Five years later, "Nakatani" virus was independently discovered in Japan, and only at a later stage it was found to be identical to the previously described Parvovirus B19[6]. First associated with human disease in 1981[7], the sero-epidemiological association between the rash illness erythema infectiosum and B19 infection in healthy children was established two years later by Anderson et al[8] .

The clinical presentation associated with B19 infection may vary greatly, ranging from benign forms of arthralgias or arthritis to life threatening conditions such as spontaneous abortion in pregnant women or temporary suppression of erythropoiesis, depending on age, im-

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munologic and hematalogic status of the host[9]. The five well-established syndromes commonly associated with B19 infection include: transient aplastic crisis (TAC)[6], fifth disease/erythema infectiosum (EI)[10], non-immune hydrops fetalis[11], arthralgia/arthritis[12] and chronic pure red blood cell aplasia (PRCA)[13].

Besides these five clinical syndromes, a wide range of rather rare diseases have been described in the literature, which association with Parvovirus B19 infection still remains unconfirmed. Among these, cutaneous[14] and cardiologic[15] manifestations, neurological disease[16], hepato-biliary disease[17], nephropathy[18] and hematological disorders[19] have been reported.

Finally, B19 virus has been implicated as the causative or precipitating agent of several autoimmune and rheumatic diseases[20,21], such as rheumatoid arthritis, juvenile idiopathic arthritis, vasculitis, systemic lupus erythematosus, systemic sclerosis, uveitis and myositis. Nevertheless, to our knowledge, there are few and discordant reports in the literature which purposely focus on the possible role of Parvovirus B19 in the pathogenesis of polymyalgia rheumathica (PMR)[22-25].

We report a case of a 74-years-old woman affected by Parvovirus B19 infection and subsequently diagnosed with PMR, presenting with low-grade fever in the evening, shoulder and pelvic girdle arthralgia and functional impairment.

CASE REPORT

The patient was admitted to our unit on May, 11th 2015, in order to investigate the sudden onset of a shoulder and pelvic girdle arthralgia associated with functional impairment and low-grade fever, for about 5 days, since few days after her return from a trip to Bali, Indonesia (April, 20th 2015). During her hospital stay, clinical, laboratory and instrumental data were collected. We performed Parvovirus B19, Dengue and Chikungunya antibody test, routine pneumotropic viruses antibody test including Influenza A and B viruses, Adenovirus, human Respiratory Syncytial virus (RSV), Chlamydia Pneumoniae and Mycoplasma Pneumoniae antibody test. Malaria, *Salmonella typhi* and *S. paratyphi*, Brucella spp., *Borrelia burgdorferi*, Leptospyra, *Anaplasma phagocytophilum*, Bartonella species (spp.), *Coxiella burnetii*, *Ehrlichia canis* and Rickettsia spp. were also investigated. Autoimmunity test (Anti-nuclear antibody-ANA, Anti-double stranded DNA-anti-dsDNA, Antineutrophil cytoplasmic antibody-cytoplasmic/c-ANCA and plasmatic/p-ANCA, Rheumatoid factor-RF, Anti-cyclic citrullinated peptide antibody-CCP, Anti-extractable nuclear antigen-anti-ENA/ ENA anti JO 1, ENA anti RNP, ENA anti SM, ENA anti SS A/Ro, ENA anti SS B/La) and routine blood investigations were carried out, including full blood count, liver function test, urea and electrolytes, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Furthermore, left scapulohumeral articulation (the main location of the pain) was examined through X-ray and an abdominal echography screening was performed.

Serum anti Parvovirus B19, Dengue, Chikungunya and pneumotropic viruses Immunoglobulin M (IgM) and G (IgG) were detected by Enzyme-linked immunosorbent assay (ELISA). Real Time Polymerase Chain Reaction (RT-PCR) test was also performed on a sample of patient's serum, with the purpose of detecting Dengue or Chikungunya virus genome. A neutralization assay for detection of Dengue e Chikungunya viruses was also carried out to confirm the immuno-enzimatic test result, according to the manufacturer's instruction. Malaria antigen and plasmodium were investigated with traditional diagnosis, based on the microscopic examination of Giemsa-stained thick and thin blood smears. Widal-Wright reaction was performed, with the purpose of searching for *Salmonella typhi* (O, H), *paratyphi* (A, B), or Brucella in patient's serum; Wright-Coombs test was also performed. Direct immuno-fluorescent assay was used to rule out anthropozoonosis: *Anaplasma phagocytophilum*, Bartonella spp, *Coxiella burnetii*, *Ehrlichia canis* and Rickettsia spp. Microagglutination antibody test for Leptospyra was performed according to the manufacturer's instruction, together with RT-PCR and Multiplex-PCR for detection of Leptospyra DNA.

Initial data from routine blood investigation showed monocytosis (11%, 900/mcl), low-grade erythrocytopenia ($3.8x10^6$ cells/mm^3) and increased levels of both ESR (60 mm/h) and CRP (5.4 mg/dl). Malaria investigations, Dengue, Chikungunya and routine pneumotropic viruses antibody test resulted negative for acute infection; conversely, influenza A and B virus screening resulted to be positive for previous infection. Data from Parvovirus B19 serology showed an increased and fluctuating title of IgG: 26.4 UA/ml at first screening, 7.7 UA/ml after two days, 21 UA/ml after 9 days from the first test (reference range: positive when > 1.1 UA/ml); IgM anti-Parvovirus B19 resulted negative.

Left scapulo-humeral articulation x-ray and abdominal echography showed no abnormalities.

The patient was finally examined by a clinical rheumatologist and, after an evaluation of all clinical, laboratoristic and instrumental data, diagnosed with PMR. Therefore, she was submitted to a daily corticosteroid oral treatment (initial regimen: prednisone oral tablets, 15 mg/day), showing a rapid response to this therapeutic regimen with a gradual and increasing reduction of the pain, together with a partial to total recovery from functional impairment.

DISCUSSION

Previous Parvovirus B19 virus infection detected by serum anti-Parvovirus B19 IgG is quite common, ranging from 2 to 15% in children between 1 and 5 years old, 15 to 60% in children 6 to 19 years old, 30 to 60% in adults, and more than 85% in the geriatric population[26]. Besides the common manifestations classically associated with Parvovirus B19 infection, such as TAC[6], EI[10], hydrops fetalis[11], arthralgia/arthritis[12] and PRCA[13], a number of other rather rare syndromes have been described in literature[14-21], but given the wide diffusion of the infection, establishing the causality of this relationship is actually quite difficult and still represents an open challenge.

Synchronous and seasonal variations of PMR with Parvovirus B19 infection have been previously observed[24,25,27] and originally lead to hypothesize a causal relationship between them. Particularly, B19 virus infection has been suspected to contribute to the aetiology of PMR before, but, nowadays, few and discordant are the reports in the literature, which purposely focus on the possible role of Parvovirus in the pathogenesis of PMR[22-26].

In fact, while some histological analysis carried out to investigate the presence of viral antigens or DNA in human tissues affected by giant cell arteritis (GCA, which association with PMR is well known[28]) reported a highly significant association between the presence of B19 DNA and histologic evidence of GCA[29], other reports in literature proved the opposite[30,31]. Nevertheless, it could be objected that succeeding in finding viral antigens within specific human tissues is not sufficient to exclude the association, since the virus usually does not persist in the same site for a long time.

In another report, Hemauer et al[22] tested the seroprevalence of IgG against VP1, VP2 (B19 viral structural proteins) and NS1 (viral non-structural protein), also investigating the association between NS1 IgG antibodies and PMR related symptoms: they concluded that Parvovirus B19 infection seemed not to be a pathogenic factor in PMR course, having found non significant differences between patients with or without NS1 IgG.

Recent research[32] revealed insights that might be useful to understand the molecular mechanisms underlying the autoimmune phenomena, which involve the inflammatory response due to cytokine activation, the formation and deposition of immunocomplexes and molecular mimicry mechanisms.

Our case may reflect, on the one hand, the possibility of misdiagnose PMR rather than a case of Parvovirus B19-related chronic arthralgia, with the main consequence of treating the patient with unnecessary steroid treatment; on the other, misdiagnosing a PMR for a viral infection may lead to a retardation of appropriate corticosteroid therapy, thus to an eventual non-desirable aggravation of clinical conditions.

Unfortunately, given the actual state of art full of conflicting data, some questions still remain unsolved: can post-infective chronic arthralgias (such as the case we reported) really be symptoms of PMR or do they rather actually only belong to chronic Parvovirus B19 infection manifestations? Where should we focus, in order to confirm or exclude, once for all, the causal relationship between B19 virus and PMR? This question might be answered by molecular biology study given that multiple mechanisms might be implicated in the pathogenesis of Parvovirus B19 triggered PMR.

Conclusions

Further and focused investigations are needed to finally shed light on the role of Parvovirus B19 infection in the development of PMR.

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Conflict of Interests

The Authors declare that they have no conflict of interests.

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