hypertension should keep the portocaval gradient or HVPG as primary end point and gold standard.

Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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A case of drug rash with eosinophilia and systemic symptoms (DRESS) induced by telaprevir associated with HHV-6 active infection

To the Editor:

We read with interest the article by Samain and colleagues [1] on the "First case of drug rash eosinophilia and systemic symptoms due to boceprevir" and would like to report herein the first case of the same syndrome, following telaprevir treatment in association with HHV-6 active infection in skin tissue.

DRESS is a severe adverse drug-induced reaction that manifests as a diffuse maculo-papular skin rash with fever, haematological abnormalities (leukocytosis, eosinophilia and/or atypical lymphocytosis) and multi-organ involvement, especially liver dysfunction [2]. The exact pathogenesis of the syndrome remains largely unknown but recently it has been associated with a T cell immune response directed towards herpes virus antigens and/or the culprit drug along with HHV-6 reactivation [3,4]. DRESS patients appear to possess low numbers of plasmacytoid dendritic cells, a leukocyte subset producing large amount of IFN-α and specialized in antiviral responses, allowing reactivation of HHVs (like HHV-6) [4]. Therefore, telaprevir as a culprit drug may trigger viral reactivations that induce a pathogenetic antiviral CD8+ immune response [2].

Moreover, HHV-6 reactivation has been linked with a more severe course of DRESS [4]. In a previously described case of telaprevir-induced DRESS, HHV-6 infection was documented only indirectly by a serological analysis (simply measuring elevation of the anti-HHV-6 antibody titre) [5] and not in the plasma and skin tissue, as it was detected in our patient. Sixteen other cases of DRESS (3 definite, 5 probable and 8 possible) induced by telaprevir [6–8] have been described from 2010 to date, but all without mentioning HHV-6 reactivation.

A 51-year-old Caucasian woman with chronic genotype 1a hepatitis C (viral load 1.8×10^6 IU/ml), complicated with fibrosis (F-2 stage, measured by ultrasonographic elastography), received treatment with the combination of interferon alfa-2a (PegIFN) and ribavirin (RBV) for four weeks, without adverse effect. Then telaprevir was added (2250 mg/daily) on April 2013 (day 0) in the absence of skin lesions. After three weeks (day 24) from the telaprevir introduction, undetectable plasma viraemia for HCV-ribonucleic acid (RNA) occurred and skin manifestations as maculo-papular itchy lesions appeared on the patient's limbs. Oral antihistamines and topical steroids were started with partial benefit but after a few days the patient worsened. Two weeks later, physical examination revealed a diffuse maculo-papular exanthem, oro-pharyngeal mucosa hyperaemia and bilateral painful axillar lymphadenopathies associated with pruritus, fever (38 °C), malaise and arthralgia. Telaprevir was discontinued and oral prednisone (0.5 mg/kg/daily) was promptly started. Cutaneous and systemic symptoms improved in a few days, whereas the blood cells count returned to normal within two weeks. Prednisone was gradually decreased and stopped in one month.

Laboratory findings showed eosinophilia (white blood cell count 5.10×10^9/L; eosinophils 19.8%, up to 1×10^9 cells/L) and lymphocytopenia (7.2%, up to 0.40×10^9 cells/L). Antibodies against cytomegalovirus (CMV), Epstein-Barr virus (EBV), and adenovirus were indicative of past infection. Bacterial and fungal culture of throat swab revealed a normal pharyngeal flora. Plasma HCV-RNA was persistently negative. Reactivation of HHV-6 was demonstrated by detection of HHV-6 cell-free serum viraemia (260 genome equivalents per ml). Anti-HHV-6 IgG antibodies proved positive (titre 1/80), while anti-HHV-6 IgM and anti-human herpes virus 7 (HHV-7) IgG and IgM antibodies were negative. Active HHV-6 infection was demonstrated also

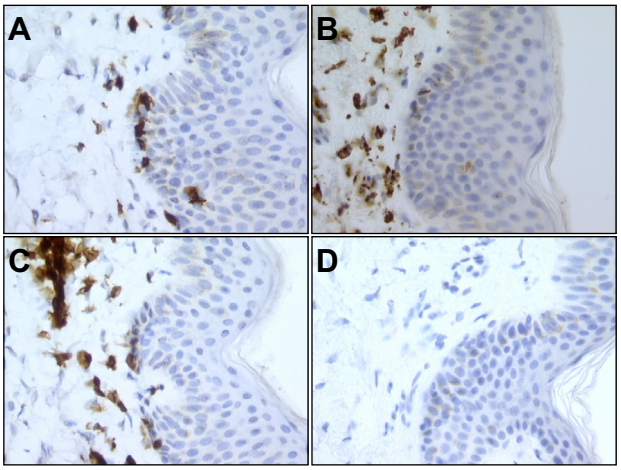

Fig. 1. Detection and localization of HHV-6 in skin lesions by an antibody panel including HHV-6 gp60/110 envelope glycoprotein, CD68, CD20, and CD3. Immunohistochemical analysis of skin tissue (streptavidin-biotin-peroxidase) showed: (A) HHV-6 gp60/110 envelope glycoprotein positivity (original magnification 63×), (B) CD68 positivity (original magnifications 40×), (C) CD3 positivity (original magnifications 40×) and (D) CD20 negativity (original magnification 20×). (This figure appears in colour on the web.)

in the skin tissue both by quantitative real-time polymerase chain reaction (qPCR) assay (3600 genome equivalents/10,000 cells) and immunohistochemical analysis with antibodies against HHV-6 envelope glycoproteins (gp60/110 kDa) (Fig. 1A). Immunohistochemical stainings revealed that HHV-6 infected cells were positive for CD68, unequivocal marker of macrophages (Langerhans cells) (Fig. 1B); conversely, they were negative for CD3 and CD20 immunostaining (Fig. 1C and D). Histopathological examination of a cutaneous biopsy showed dermal perivascular inflammatory infiltrate, composed of lymphocytes and histiocytes with scattered eosinophils in the dermis, consistent with a drug reaction. Diagnosis of DRESS was confirmed by the presence of all seven diagnostic criteria, established in 2006 by the Japanese Research Committee on Severe Cutaneous Adverse Drug Reaction (J-SCAR): maculo-papular skin rash, developing at least 3 weeks after starting therapy, with a limited number of drugs, prolonged clinical symptoms after discontinuation of the causative drug, lymphadenopathy, fever (>38 °C), leukocyte abnormalities (leukocytosis, atypical lymphocytosis, eosinophilia), liver abnormalities, HHV-6 reactivation [9].

In order to decrease the rate of severe drug reactions in HCV patients receiving new anti-HCV drugs, a rash management plan has been developed: only in cases of a generalized rash (involving more than 50% of the body surface area) and in life-threatening or systemic reactions (like DRESS), telaprevir must be immediately stopped and systemic corticosteroid treatment is required [10].

In conclusion, we report, to our knowledge, the first case of telaprevir-induced DRESS associated with HHV-6 reactivation: active HHV-6 infection was also documented in some skin tissue resident macrophages (Langerhans cells). We also emphasize the increased risk for DRESS in telaprevir-treated patients that requires particular vigilance for the unpredictable and potentially life-threatening evolution of this syndrome.

Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

Authors' contributions

All authors have equally contributed in study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, administrative, technical and material support.

Acknowledgments

We would like to thank Dr Roberta Zappacosta and Dr Marcella Liberatore for their work in the search of HHV-6 and HHV-7 active infection on skin and serum samples.

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