Unusual rash accompanied by enterovirus infection and human bocavirus co-infection in a 9-week-old infant in Cologne, Germany

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Introduction: The family Picornaviridae is divided into several genera, including the genus Enterovirus, which includes the species Human enterovirus A to -C and Human rhinovirus A to –C. These viruses are frequently associated with respiratory and gastrointestinal diseases. Coxsackie virus and echoviruses can induce a rash in children, such as hand-foot-and-mouth disease caused by coxsackie virus A16, while rhinoviruses are associated mainly with respiratory infections.

Case presentation: We describe a clinical case of mild rhinitis in a 9-week-old female infant with HBoV and enterovirus co-infection accompanied by an unusual rash that strongly resembled granuloma annulare, having plaques with raised non-scaly erythematous borders. The child was afebrile, displayed a garland-like rash that within minutes changed its pattern and had moderately elevated expression of tryptase. No other pathogens were detected.

Conclusion: It was concluded that the rash originated from the double infection with enterovirus and HBoV, as no further rash-associated pathogens were detected. The case is important as it is the first description, to the best of our knowledge, of this unusual rash seen with enterovirus/HBoV co-infection, and as this condition should be taken into account in future.

Keywords: Elevated tryptase expression; enterovirus infection; human bocavirus infection; subfebrile body temperature; unusual rash.

Introduction

Enteroviruses belong to the family Picornavirus and frequently infect all age groups. In children in particular, mild infections causing upper respiratory tract symptoms such as rhinitis, mild cough and mild rash, especially in the mucosal regions, are frequent and belong to the common cold diseases. Although symptom-free episodes of enterovirus and rhinovirus infections are also common (Byington et al., 2015), infection in childhood is mostly accompanied by clinical symptoms. The case presented in this report is important as it was accompanied by unusual strong and garland-like rash, together with elevated tryptase expression, and could have led to a wrong diagnosis, although the child’s wellbeing was not measurably affected; based on the clinical findings and the rash, an allergic disease could have been diagnosed, although no allergic reactions could be confirmed. Both the rash and the mild rhinitis could have been caused by the double infection with human bocavirus (HBoV) and enterovirus. To the best of our knowledge, this combination of co-infection has not been described for very young infants.

Case report

The patient was a 9-week-old female infant who was admitted to our hospital because of an unusual exanthema resembling granuloma annulare, comprising plaques with raised non-scaly erythematous borders. On admission, it was reported that the child had been restless the previous day, with reduced drinking volumes, and displayed symptoms of an upper respiratory tract infection. On the morning of admission to the hospital, the non-itchy rash occurred for the first time on her hands and arms. The rash changed its position over the course of the day with increasing flares and decreasing areas. No acute or chronic illness was reported in the family history. The child had not received any vaccinations at the time of admission, and the pregnancy and birth were uncomplicated.

On clinical examination, the child was a well-developed female infant in good average condition with a subfebrile
temperature. No signs of meningitis were observed, and no internal diseases were identified; the fontanelle was within normal limits, and no relevant lymphadenopathy was detected. The oral mucosa was moist, the throat and pharynx were asymptomatic, the tonsils were normal, and the left and right tympanums were also free of symptoms. The exclusive clinical symptom on admission – besides the rash – was a mild rhinitis.

The skin displayed multiple irregular garland-like exanthema over the whole body (Fig. 1), which did not affect the oral mucosa. The left upper lid was reddened and moderately swollen. Surprisingly, the exanthema changed its locations and size, often within minutes.

During her stationary stay in hospital, the infant remained afebrile, had a stable cardiorespiratory condition and did not appear ill, despite the rash. By day 3, the exanthema had nearly vanished and the infant was released from the stationary observation.

**Investigations**

The differential blood count was normal, no inflammation parameters were observed and the results of clinical chemistry investigation of the blood and urine were in the normal ranges and did not show any indication of affected organs. The sole elevated enzyme was trypase, which peaked at 23.1 \( \mu g \cdot l^{-1} \) (normal, <11.4 \( \mu g \cdot l^{-1} \)), but this peak normalized within 1 week, decreasing to 5.6 \( \mu g \cdot l^{-1} \).

Microbiological investigations included PCR screening of the serum for parvovirus B19, Epstein–Barr virus and *Mycoplasma*, all with negative results. The serum was tested by our external laboratory provider. Investigation of a nasopharyngeal wash with the Respifinder SMART 22 assay and the Meningofinder 7 Custom Plus Assay (which includes test for includes mumps and measles virus in addition to the standard Meningofinder assays) (both assays from Pathofinder) revealed negative results except for the detection of enterovirus RNA and HBoV DNA. Unfortunately, due to the age of the patient, no residual serum was available for detection of a putative HBoV viraemia.

Unfortunately, due to the limited amount of nasopharyngeal wash and the lack of residual serum, no in-depth serotyping of the enterovirus was performed. As the symptoms rapidly resolved, it was decided not to sample further specimens in order to reduce the burden for the patient. However, due to the assay specifications of the Respifinder and Meningofinder assays, it was concluded that HBoV-1 was detected (the Respifinder Assay is specific for HBoV-1) and that an enterovirus but not a rhinovirus was detected, as both assays detect enterovirus but the Meningofinder would not have been positive if a rhinovirus was present.

**Diagnosis**

Based on the laboratory investigations, the patient’s age and the clinical signs, the most likely diagnosis was a

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**Fig. 1.** Garland-like rash on the side (a) and back (b) of the patient during the first 2 days of stationary observation. The rash decreased at day 3 and vanished completely after 1 week.
respiratory enterovirus infection accompanied by an HBoV infection. This diagnosis was congruent with the clinical signs of rhinitis. The unusual rash was most likely caused by the viral infection, but due to its shape remained a matter of speculation and deserved description.

**Treatment**

No treatment was required.

**Outcome and follow-up**

The patient was released from the stationary observation on day 3 after the onset of the exanthema and had recovered fully within 1 week.

**Discussion**

Although the case was characterized by mild clinical symptoms, the garland-like rash in concert with the detection of enterovirus RNA and HBoV DNA in the nasopharyngeal wash is worthy of being reported. The rash was characterized by a pattern that changed within minutes, a phenomenon we were not aware of and that, to the best of our knowledge, has not described previously in the literature. Besides the unusual behaviour of the exanthema, it was surprising that the infant appear not to be affected by the rash and that the exanthema vanished as quickly as it had appeared. Moreover, the rash could not be attributed to any other pathogen known to cause exanthema and thus most likely was caused by the enterovirus infection and/or the HBoV co-infection. However, this conclusion remains a matter of speculation, and should be confirmed by future analyses and clinical observations, if possible.

The sole parameter that was not within normal ranges was the elevated tryptase, which is generally used as a marker for systemic mastocytosis (Carter *et al.*, 1995), a condition that was not present in the infant. Consequently, the isolated increase in tryptase could have led to a wrong diagnosis and treatment of the patient.

Elevated tryptase levels have been described most recently as a marker for severe and/or milk-induced anaphylaxis (De Schryver *et al.*, 2015). However, no further clinical expression of anaphylaxis were observed, and thus the elevated tryptase levels may have had a different cause.

Elevated tryptase expression is also a marker for an increased risk of anaphylactic reactions after insect bites (Yavuz *et al.*, 2013), also a condition that did not apply to our patient. However, the elevated tryptase levels could also be due to the viral infection, as described previously for respiratory tract infection: the normal elevation of tryptase expression induced by allergic reactions ranges from 25 to 1000 µg l⁻¹, but a mild increase in tryptase expression was observed after an experimental rhinovirus infection (Calhoun *et al.*, 1991), and was also described in 11 of 12 children infected with respiratory syncytial virus (Everard *et al.*, 1995).

In contrast, no change in the tryptase expression before and after a rhinovirus infection was observed after exposure to aerosolic allergens by Greiff *et al.* (2002). Animal studies have confirmed that tryptase induction can be initiated by viral infections, such as H5N1 in mice (Hu *et al.*, 2012), Newcastle disease virus in birds (Sun *et al.*, 2009), bursal disease in chickens (Wang *et al.*, 2008) and bovine respiratory syncytial virus in cattle (Jolly *et al.*, 2004). Thus, the elevated level of tryptase expression in our patient supports the hypothesis that it was associated with the picornavirus infection and supports the assumption that the irregular exanthema is a (possibly novel) phenomenon that could occur during the acute double infection of HBoV and enteroviruses. It should be noted in this context that the human parvovirus that has been known for the longest time, parvovirus B19, which causes fifth disease or erythema infectiosum, frequently causes exanthema that appears in similar shapes to that in the present case. It is also possible that the rash originated from infected or destroyed mast cells that released tryptase as a consequence of the HBoV/enterovirus co-infection.

A further option would be that the exanthema resulted from the infection with either of the pathogens alone. In this context it is worth noting that two studies on the clinical characteristics of HBoV infections did not find such exanthema in HBoV mono- or co-infected patients (Esposito *et al.*, 2008; Karalar *et al.*, 2010), whereas a different rash, namely petechial exanthema, was frequently observed in mixed respiratory infections by another group (Schneider *et al.*, 2013).

In conclusion, to the best of our knowledge, the present clinical observations in such a young infant in concert with HBoV/enterovirus co-infection have not been described so far in the literature and should be considered in future clinical investigations.

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**References**


