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Vernal keratoconjunctivitis and eosinophilic esophagitis: A rare combination?

Maria Cristina Artesani, MD[a]*, Sara Urbani, MD[a], Carla Riccardi, MD[a], Mariacristina Esposito, MD[b], Paola De Angelis, MD[c], Francesca Rea, MD[c], Renato Tambucci, MD[c], Monica Malamisura, MD[c], Luca Buzzonetti, MD[b] and Alessandro Giovanni Fiocchi, MD[a]

ABSTRACT

Vernal keratoconjunctivitis (VKC) is a bilateral ocular inflammatory disease with a conjunctival and corneal involvement and typical onset during childhood. Eosinophilic esophagitis (EoE) is a chronic disease characterized by eosinophilic inflammation of the mucosa (≥15 eosinophils/HPF) and symptoms of esophageal dysfunction. EoE and VKC are both immune-mediated diseases sharing a similar pathogenetic mechanism and a high association with other allergic diseases. Nevertheless, no data are currently available about their clinical association. We present 4 cases of concomitant diagnosis of vernal keratoconjunctivitis and eosinophil esophagitis suggesting that these conditions may coexist in the same patient more frequently than expected. Health care providers should be aware of the possibility of co-occurrence in their daily practice.

Keywords: Vernal keratoconjunctivitis, Eosinophilic esophagitis, Th-2 disease, Allergy

Vernal keratoconjunctivitis (VKC) is a bilateral ocular inflammatory disease with a conjunctival and corneal involvement and typical onset during childhood.[1] Eosinophilic esophagitis (EoE) is a chronic disease characterized by eosinophilic inflammation of the mucosa (≥15 eosinophils/HPF) and symptoms of esophageal dysfunction.[2]

EoE and VKC are both immune-mediated diseases sharing a similar pathogenetic mechanism and a high association with other allergic diseases. Nevertheless, no data are currently available about their clinical association. To our knowledge, we report the first 4 cases of paediatric patients with a concomitant diagnosis of VKC and EoE.

The Vernal Keratoconjunctivitis Multidisciplinar Outpatient of our Hospital follows in a coordinated manner, with the presence of an ophthalmologist and an allergist, the children affected by VKC. The diagnosis of VKC is given by an ophthalmologist based on subjective ocular symptoms, such as itching, burning, photophobia, tearing and foreign body sensation, in association with typical ocular signs like conjunctival hyperemia, tarsal/limbal papillae, giant papillae, corneal involvement (Fig. 1). Between October 2019 and December 2022, 4 patients were diagnosed with EoE. All were Caucasian male with a median age of 4.5 years (range 2–9) at VKC onset and 8 years (range 5–11) at EoE diagnosis. The clinical patients' presentations are summarized in Table 1. All patients presented with concomitant asthma at diagnosis, 2 of them had allergic rhinitis, 1 patient had an IgE-mediated food allergy (IgE-FA) to fish

[a]Allergy Unit, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy.
*Corresponding author. Allergy Unit, Bambino Gesù Children's Hospital, IRCCS, Piazza Sant'Onofrio, 4 00165 Rome, Italy. E-mail: mariac.artesani@opbg.net
Full list of author information is available at the end of the article

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and tree nuts, and 1 patient had an asymptomatic sensitization to milk, white egg, and lipid transfer protein.

The patients also presented a variable aeroallergen sensitization pattern investigated by skin prick test. All were treated with cyclosporine for VKC, and periodic follow-up visits were scheduled. After a period ranging from 3 to 4 years, we diagnosed EoE to these patients. Two patients reported dysphagia as onset symptom, 1 of whom had a food impact treated in emergency room. Patient 3 referred abdominal pain and heartburn, while Patient 1 presented abdominal pain associated with blood and mucus in the stools. All patients underwent an endoscopy, with macroscopical findings suggesting for EoE, such as white exudates, furrows, edema (Fig. 1), and with a peak count >15 eosinophils/high power field (HPF) at biopsy.[2] We found exclusively inflammatory phenotypes of EoE without fibrotic characteristics, likely due to the short interval between symptom onset and endoscopic diagnostic confirmation. Furthermore, Patient 1 performed a colonoscopy with a concomitant diagnosis of eosinophilic colitis (peak count 87/HPF). In our experience, the reported cases represent approximately 1.7% (4/230) of patients diagnosed with VKC in the considering period.

Although they are 2 different conditions that affect different organs, there are certain similarities between EoE and VKC that need to be emphasized. First, both diseases have demonstrated genetic predisposition as shown by familial clustering, twins' concordance and common genetic loci risk linked to the upregulation of the cytokine gene cluster on chromosome 5q.[1,3]

Second, both diseases characteristically affect young males with a similar ratio (M:F = 3:1).[4,5] Evidence suggests a hormonal role in the pathogenesis of VKC, which may explain the higher incidence in males.[1] However, this aspect is less investigated in EoE, where the evidence suggests a role of 17-Beta Estradiol in down-regulation of IL-13 functions.[6]

Third, both VKC and EoE are quite rare conditions and therefore underdiagnosed and under-recognized and share similarities in their increasing rates of incidence and impact on the quality of life of affected patients.

Furthermore, both conditions usually exhibit a characteristic seasonal pattern, with a clinical exacerbation occurring during peak pollen periods, proving that aeroallergens exposure could represent a crucial factor in their pathogenesis. Epithelial barrier impairment is a hallmark feature of these diseases that allow allergens to penetrate trough a misfunctioning barrier and to elicit TH2 response. Several cytokines have been implicated in their pathogenesis, including thymic stromal lymphopoietin (TSLP), interleukin (IL)-4, IL-5, and IL-13.[1,4] These cytokines are involved in the development of Th2-mediated immune responses and play a crucial role in promoting eosinophilic infiltration and activation. Indeed, similarly to EoE, the presence of eosinophils in conjunctival cytology has been proposed as a marker to confirm the diagnosis of VKC and to monitor the response to treatments.[7]

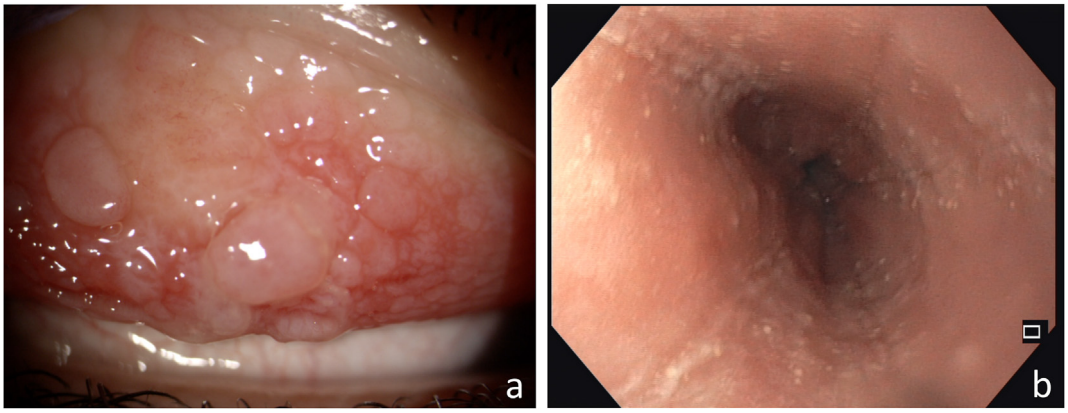

Fig. 1 Ocular and esophageal clinical presentation of Patient 4. A) Cobblestone-like giant papillae on the upper tarsus. B) Longitudinal furrows and white exudates in the proximal esophagus.

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4
Sex	Male	Male	Male	Male
Comorbilities				
Allergic rhinitis	No	Yes	No	Yes
Asthma	Yes	Yes	Yes	Yes
Atopic dermatitis	No	Yes	No	No
History of IgE-FA	No	Yes	No	No
EoG	No	No	No	No
EoC	Yes	No	No	No
Positive skin prick test				
Aereoallergens	pollen of grasses and olive	dust mites	pollen of grasses, olive, cypress	pollen of grasses, olive, halzenut tree
Foods	None	fish, tree nuts	None	milk, white egg, lipid transfer protein
Characteristic of VKC				
Age at diagnosis, y	2	3	6	9
Presenting symptoms				
Itching	Yes	Yes	Yes	Yes
Foreign body sensation	Yes	Yes	Yes	No
Photophobia	Yes	Yes	Yes	Yes
Tearing	Yes	Yes	Yes	Yes
Presenting signs				
Palpebral conjunctiva papillae	0	2	1	3
Bubar conjunctiva hyperemia	3	2	1	3
Giant papillae	3	0	0	3
Limbus Tantra's dot	2	2	1	0
Corneal epitelial sign	1	0	0	0
Characteristic of EoE				
Age at diagnosis, y	5	7	9	11
Presenting symptoms[a]				
Abdominal pain	Yes	No	Yes	No

(continued)

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4
Nausea, vomiting	No	No	No	No
Heartburn	No	No	Yes	No
Dysphagia	No	Yes	No	Yes
Food impact	No	No	No	Yes
Endoscopy findings at diagnosis				
Edema	No	Yes	No	1
White exudates	Yes	Yes	No	1
Furrows	No	Yes	No	0
Rings	No	No	No	1
Stricture	No	No	No	0
EREFS score[9]	1	4	0	3
Histological findings at diagnosis				
Peak eosinophils count	39	80	>100	>100
Basilar hyperplasia	No	Yes	No	No
Papillae hyperemia	Yes	Yes	Yes	Yes
Microabcess	Yes	Yes	Yes	Yes
Fibrosis	No	No	No	No

Table 1. (Continued) VKC and EoE clinical patients'presentations. *IgE-FA=IgE-mediated food allergy; EoG = eosinophilc gastritis; EoC = eosinophilic colitis. [a]VKCpresenting symptoms was graded according to Bonini grading scale*[10]

Additionally, EoE and VKC are both characterized by a chronic inflammation and tissue damage and remodeling. A recent transcriptomic analysis of conjunctival epithelial demonstrated that VKC cells exhibited elevated expression of pro-inflammatory genes, such as IL-6, CCL24, CCL18, CXCL1, ICAM-1, and TGFβ-1.[8] This increase in gene expression was found to be associated with an increase in disease severity score and corneal staining, indicating the presence of epithelial dysfunction in VKC. These findings suggest that the pro-inflammatory response and tissue damage seen in VKC may be driven by similar mechanisms as those involved in EoE.

Indeed, in EoE, TGF-β, IL-13, and TNF-α have the potential to stimulate myofibroblast differentiation, to promote the synthesis and contraction of extracellular matrix proteins, and to trigger epithelial-mesenchymal transition (EMT), ultimately leading to esophageal subepithelial fibrosis.[4]

In eosinophilic esophagitis, chronic damage macroscopically manifests as fibrosis and stricture formation with consequent esophageal dysmotility and higher food impact risk. Similarly, in VKC giant papillae represent a morphologic expression of fibroblast activation and tissue remodeling and they can lead to punctate keratopathy, to progression of corneal epithelial defects and ultimately result in shield ulcers.

However, it is noteworthy that although VKC is typically a self-limiting condition with a high incidence of spontaneous symptom resolution at puberty, EoE follows a chronic and relapsing course with a possible recurrence and remission phases.

In conclusion, much remains to be elucidated regarding the existence and nature of an association between VKC and EoE. Our findings suggest that these two conditions may coexist in the same patient more frequently than expected. Further validation of the observed association should be pursued through rigorous and expansive epidemiologic studies involving larger patient populations.

However, health care providers should be aware of the possibility of co-occurrence in their daily practice. This association could have significant implications for the management and treatment of affected patients. Further evidence is needed to understand the reciprocal relationship between these diseases and to identify shared target molecules in order to develop effective strategies in managing patients with concomitant diagnosis of EoE and VKC.

Abbreviations

VKC, (Vernal KeratoConjunctivitis); EoE, (Eosinophilic Esophagitis); (IgE-FA), IgE-mediated Food Allergy; HPF, (High Power Field); EMT, (Epithelial-Mesenchymal Transition); TSLP, (Thymic Stromal Lymphopoietin); EoG, (Eosinophilic Gastritis); EoC, (Eosinophilic Colitis).

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Availability of data and materials

Data and materials are available.

Author contributions/custom author support

Maria Cristina Artesani: Conceptualization (lead); Data curation (lead); Investigation (equal); Writing-original draft (equal).
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Mariacristina Esposito: Investigation (equal); Supervision (equal).
Carla Riccardi: Supervision (supporting), Investigation (equal).
Paola de Angelis: Supervision (supporting), Investigation (equal).
Francesca Rea: Supervision (supporting), Investigation (equal).
Renato Tambucci: Supervision (supporting), Investigation (equal).
Monica Malamisura: Supervision (supporting), Investigation (equal).
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Alessandro Giovanni Fiocchi: Supervision (supporting).

Ethics approval and consent to participate

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Consent for publication

Authors consent to publication.

Declaration of competing interest

Authors disclose any Competing interests related to the manuscript content.

Author details

[a]Allergy Unit, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy. [b]Ophthalmology Unit, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy. [c]Digestive Endoscopy and Surgery Unit, Bambino Gesù Children's Hospital-IRCCS, Rome, Italy.

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