Toward a potential association between eosinophilic esophagitis and Klinefelter syndrome: a case series and review of the literature

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Abstract: Klinefelter syndrome (KS) is a sex aneuploidy abnormality comprised by one additional X chromosome. It occurs in 1:500–1000 male births. As with women, an increased susceptibility to autoimmune diseases is present. We report three cases of coexisting EoE and KS for a prevalence of 2% in our EoE clinic. Possible changes in gene expression in KS are reviewed, some of which may be related to activation of genes located on the X chromosome. We postulate that these X-activated genes in patients with KS yield a greater likelihood of developing EoE because of their genetic predisposition to autoimmune diseases.

Keywords: eosinophilic esophagitis, klinefelter syndrome, sex aneuploidy, dysphagia

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Introduction
Klinefelter syndrome (KS) is the most common disorder of male sex aneuploidy, consisting of an additional X chromosome and occurring in 1 in every 500–1000 male births. Several disorders and a higher risk of autoimmune diseases have been reported in KS.1

Eosinophilic esophagitis (EoE) is a chronic, immune-mediated disorder occurring in 1 in 2000 people.2 Although antigens play a pivotal role in EoE, a genetic predisposition has been demonstrated.2 A potential pathogenic contributing role of genes located on the X chromosome has been suggested despite male predominance.3

We recently identified three subjects with KS among our cohort of 150 male adult EoE patients (Table 1). CARE guidelines and checklist were applied in data collection process and drafting of the article. The aim of this work was to describe these three patients and to review the literature for similar cases yielding a possible pathophysiological explanation.

Case summaries

Case 1
A 15-year-old KS male, with atopy and food allergies presented to our hospital with chest pain, dysphagia, and hematemesis. Computed tomography and esophago-gastro-duodenoscopy (EGD) demonstrated an esophageal dissection that was treated conservatively. Biopsies confirmed EoE diagnosis prompting administration of oral systemic steroids and a hypoallergenic diet. Subsequently, starting long-term treatment with topical fluticasone effectively maintained remission.4

Case 2
A 16-year-old male was admitted to a community hospital for severe malnutrition due to a long history of dysphagia, odynophagia, and chest pain. EGD revealed edema and trachealization of the esophagus; multiple biopsies from the distal and proximal esophagus (18 eos/HPF) confirmed a diagnosis of EoE. In the setting of concordant
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Table 1. Demographic and clinical features of the three patients with EoE and KS.

|                      | Case 1                          | Case 2                          | Case 3                          |
|----------------------|---------------------------------|---------------------------------|---------------------------------|
| Age at diagnosis, years | 15                              | 18                              | 34                              |
| Gender               | Male                            | Male                            | Male                            |
| Symptoms at diagnosis | Acute chest pain with dysphagia and hematemesis | Dysphagia with severe malnutrition | Dysphagia and bolus impaction |
| Allergic comorbidities | No                              | Atopic dermatitis and rhinoconjunctivitis | Asthma                          |
| Peripheral eosinophilia | Yes                             | Yes                             | Yes                             |
| Peripheral eosinophils (cells × 10⁹) | 0.31                           | 0.5                             | 0.48                            |
| IgE levels (kU/L) [0–120] | 173                             | 1250                            | Not assessed                    |
| Food Allergies       | Several, including nuts and fish [SPT and RAST] | Several, including wheat and milk proteins [RAST] | Not assessed                    |
| EREFS                | E1R0E1F1S0                      | E1R1E0F0S0                      | E0R1E0F1S0                      |
| Eos/HPF on esophageal biopsies | >15 eos/HPF                     | 18 eos/HPF                      | 40 eos/HPF                      |
| Treatment response [PPI, STC, and elimination diet] | Steroid responder             | Steroid responder              | Steroid responder              |
| KS genotype          | 47, XXY                         | 47, XXY                         | 47, XXY                         |
| Symptoms that led to KS diagnosis | Minor developmental and learning disabilities | Minor developmental and learning disabilities | infertility                   |
| Serum level of testosterone | 3.2 ug/L [3–8]                 | 2.9 ug/L [3–8]                 | 334 ng/dL (240–827)            |
| Serum level of estradiol | 35 pg/mL [10–80]               | 26 pg/mL [10–80]               | 33 pg/mL (<40)                 |

EoE, eosinophilic esophagitis; eos, eosinophils; EREFS, the eosinophilic esophagitis (EoE) endoscopic reference score; E, edema; R, rings; E, exude; F, furrows; S, stricture; HPF, high-power field; KS, Klinefelter Syndrome; PPI, proton pump inhibitor; RAST, RadioAllergoSorbent test; SPT, skin prick test; STC, swallowed topical steroids.  
*Normal values differ according to different laboratories.*

endocrine evaluations, sexual hormonal imbalance led to karyotype evaluation and KS diagnosis. The patient started swallowed fluticasone with clinical benefit and histological remission.

**Case 3**

A 34-year-old male with asthma was diagnosed with KS during couple-infertility assessment. He had a long history of dysphagia with compensatory behaviors and three episodes of food bolus impaction including an episode requiring endoscopic removal. Endoscopy revealed a narrow mid-esophagus with subtle trachealization and furrows. Histology revealed 40 eos/HPF. He is in clinical and histological remission once starting swallowed fluticasone treatment.

**Discussion**

In this case series, we reported three KS patients with a diagnosis of EoE and speculate a
relationship to EoE. With a prevalence of 1:2000 for EoE and 1:1000 for KS; the statistical overlap between these two disorders should be quite low. In our population of EoE patients, there was a prevalence of 2% for overlapping KS and EoE. In the literature, another case report of an EoE male with KS and a case series of 19 patients having both sex chromosome aneuploidies and EoE (47XXY (n=8), 48XXYY (n=4), 47XXX (n=3), 47YYY (n=3), 48XXXY (n=1)) have been reported. Clinical presentation resembled that of other EoE patients and the calculated prevalence of EoE was 60 times greater than in the general population (3% vs 0.05%). Furthermore, when compared to men with a normal genotype, KS presents an increased risk of autoimmune and atopic diseases including higher rates of asthma and allergic disorders. An increased risk may be related to an X-related KS genotype. For example, although the extra X chromosome is suppressed in KS, 5–15% of X-chromosomal genes escape inactivation and are expressed from both X chromosomes. In KS, the extra copies of the ‘escaped genes’ lead to a surplus of gene products that have been linked to a pro-autoimmune background. This may be contributed by a greater regulation of miRNAs that affect immune function in women (10%) when compared to normal Y-chromosome men (4%). It is estimated that miRNAs regulate 30–50% of all protein-coding genes, so their potential role is relevant. Lu et al. reported 32 miRNAs specific for untreated EoE, with upregulation of miRNA-21 and miRNA-223 linked to the EoE transcriptome. Furthermore, some interleukins and several members of the toll-like receptor (TLR) family are located on the X chromosome. TLR7 overexpression is critical in autoimmune disorders such as systemic lupus erythematosus. TLR7 recognizes single-stranded RNA, promotes B-lymphocytes activation and production of pro-inflammatory cytokines. In immune cells of KS males, an increase in the TLR7-driven response is unmasked due to failure of normal X chromosome inactivation. In addition, activated TLR7 promotes eosinophil survival and production of cytokines. Intrestingly, other TLRs (TLR1,2,9) are overexpressed on biopsies from active EoE patients. Among other X-linked gene functions, forkhead box P3 (FOXP3) modulates regulatory T cells (Treg) production and function, while CD40 ligand (CD40 L) modulates an adaptive immune response regulating lymphocytes survival and activation. Le-Carlson et al. demonstrated the presence of CD40 L on T-cells that interact with CD40 on eosinophils in the esophageal mucosa of EoE patients, suggesting their role as antigen-presenting cells (APCs). Finally, estrogen promotes a pro-inflammatory Th2 response and increases the major histocompatibility complex (MHC) II expression on APCs. In contrast, testosterone augments Th1 response and increases the production of anti-inflammatory cytokines. This may be relevant as KS patients have a cytokine profile similar to females, slightly lower testosterone levels and a relative hyperestrogenism when compared to healthy men. In EoE, thymic stromal lymphopoietin (TSLP) and its receptor (TSLPR) encoded on the X chromosome act by regulating Th2 responses and have been identified as a potential susceptibility marker for EoE. Accordingly, food allergens could trigger TLR 3 signaling, inducing TSLP and causing the activation of the Th2-pathway seen in EoE. More recently, Kottyan et al. identified another EoE risk locus at Xq28, encoding the genes vacuolar ATPase Assembly Factor 21 (VMA21) and G Protein-Coupled Receptor 50 (GPR50). A summary of potential mechanisms is shown (Figure 1).

In conclusion, we postulate an association of KS and EoE. This association is based on this and a prior case series, suggesting a higher prevalence of EoE in KS. As important, the influence of the extra X chromosome (s) could be associated with multiple key genomic and epigenetic pathways, leading to the upregulation of Th2 response and a greater predisposition to autoimmune diseases. Further research into this group of patients could yield greater insight into the pathogenesis of EoE.

Author contributions
Matteo Ghisa: Conceptualization; Data curation; Methodology.
Vincenzo Savarino: Conceptualization; Data curation; Methodology.
Andrea Buda: Conceptualization; Data curation; Methodology.
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Ethics approval
All patients with eosinophilic esophagitis followed at our center are included in a registry approved by our EC (Identifier: Cesc 3312/10/A0/14). Each
patient signed a written informed consent to be included in this registry and approved the use of their data for research purpose.

**Patient signed consent**
Signed informed consent has been obtained from each patient, for data collection, and publication.

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