

Chronic urticaria can be caused by cancer and resolves with its cure

Dear Editor,

We read with great interest the letter of Larenas-Linnemann et al¹ concerning chronic urticaria (CU) caused by malignancy and healed after antineoplastic treatment. We agree with the authors that the link between CU and cancer is unclear.¹

In our experience, the occurrence of CU in patients with neoplastic diseases is very rare. Herein, we report data from a retrospective evaluation of consecutive patients with CU who were referred to Dermatology Unit of the University of Naples Federico II from January 2008 to December 2016. The study was approved by Ethical Committee. A total of 1493 patients (697 males, 46.7%, and 796 females, 53.3%; mean age 48.3 ± 18.1 years) were enrolled. They all signed an informed consent. According to the EAACI/GA²LEN/EDF/WAO guidelines,^{2,3} in all patients, complete blood count, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) were performed. Furthermore, based on the medical history, 182 (12.2%) patients were screened with thyroid function tests [including thyroid-stimulating hormone (TSH), free thyroxine (fT) 4 and 3, antithyroglobulin Ab, antithyroperoxidase Ab], 178 (11.9%) with chest X-ray, 102 (6.8%) with abdominal ultrasound, 92 (6.2%) with prostate specific antigen, 91 (6.1%) with stool test, 83 (5.7%) with mammography, and 65 (4.5%) with lymphonodular ultrasound. Only in 1 of 1493 (0.007%) patients, we found CU most likely associated with cancer. It was a 62-year-old woman with CU lasting 4 months and unresponsive to antihistamines, used up to quadruple dose. The patient referred temporary and incomplete improvement after treatment with oral prednisone. Because of weight loss in the last 2 months, laboratory workup (including fT3, fT4, TSH, antinuclear antibodies and abdominal ultrasound, other than blood count, ESR, CRP) was normal. On the other hand, chest X-ray showed a large atelectasis of the upper lobe of the right lung and an elevation of homolateral hemidiaphragm, due to a hilar mass. Lung computed tomography scan and biopsy confirmed the diagnosis of small cell cancer. Chemotherapy was started and CU disappeared after the first session of treatment. At the present time, the patient is in remission from cancer and is free from hives.

About one quarter of malignancies found linked with CU are papillary carcinomas of thyroid. Moreover, hematologic, gastrointestinal, breast, testicle, prostate, ovarian, or brain malignancies have been sporadically reported.¹ CU has been associated with cancer of the lung in 4 cases,¹ in 1 case only with small cell carcinoma.⁴ In agreement with Larenas-Linnemann et al, cancer-associated CU seems to have some peculiar characteristics: (i) patients

are resistant to antihistamine treatment, while only oral corticosteroids lead to temporary improvement; (ii) the mean duration of CU is 2-8 months before detection of malignancy; (iii) CU resolves in few weeks after the start of chemotherapy; and (iv) the recurrence of urticaria may be the expression of cancer relapse.¹ Malignancy might induce immune dysregulation and hormonal abnormality with subsequent complement activation or alteration in the coagulation pathways, both related to CU.^{1,5} We believe that the effect of medications commonly used for CU is not remarkable on cancer development, as antihistamines do not seem to have oncogenic activity and the CU duration is relatively short before the discovery of the malignancy.

We would like to thank Larenas-Linnemann et al for their contribution to literature with such an excellent paper. The cases reported in the literature are anecdotal; instead, our data cover a large cohort of 1493 consecutive CU patients and seem to confirm the rarity of the association (0.007% of our patients). Notwithstanding, a careful medical history should be taken in all patients with antihistamine-resistant CU, as cutaneous disease may sometimes be the only clinical expression of malignancy. Therefore, in these cases an appropriate diagnostic course should be performed according to clinical features.

CONFLICTS OF INTEREST

None declared.

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On the pathogenicity of the plasminogen K330E mutation for hereditary angioedema

To the Editor,

Bork et al.¹ recently reported the segregation of the heterozygous K330E (c.988A>G, p.Lys330Glu) variant of the plasminogen gene (PLG) in 4 families with hereditary angioedema (HAE) with normal C1-inhibitor (C1-INH) and without HAE-specific F12 mutations (unknown HAE, U-HAE). Although familial segregation argues strongly in favor of the disease causality of a given variant, this is not enough on its own to prove its pathogenicity.²

After genotyping angioedema patients using of a custom NGS platform targeted on 55 genes encoding for proteins of the contact system, we detected 6 carriers of the PLG-K330E variant. Our findings indicate that this variant might be not the only causal alteration at least when heterozygous. The first case is a homozygous 75-year-old Greek woman with severe angioedema (18 attacks/year when out of prophylactic treatment) since her age of 40 years. The only effective treatment is tranexamic acid. Her family history is free and her two healthy daughters, aged >45 years, are heterozygous carriers of the variant. Another patient is a 65-year-old Bulgarian woman without family history of angioedema who, since her age of 41 years, has experienced 5 severe attacks involving tongue and larynx. She is heterozygous for the PLG-K330E variant but she is also carrier of a not-yet-reported carboxypeptidase N variant (c.931T>C, p.Cys311Arg) predicted as deleterious.³

Two more Spanish U-HAE patients belonging to the same family (father and daughter) were found heterozygous for the PLG-K330E variant. The father, died at his age of 94 years, suffered his first attack at the age of 75 after receiving an ACE-inhibitor. A second attack appeared at his age of 83 after he received dutasteride for benign prostatic hyperplasia. Thereafter, he suffered, every 2-3 months, mild nondrug-induced attacks controlled by tranexamic acid. His daughter, 62 year old, firstly experienced an attack during her only pregnancy and afterward she had at least two moderate attacks of tongue swelling. Her daughter (granddaughter of the proband) suffers several severe estrogen-induced attacks affecting tongue, lips, and larynx, but she has not been genotyped as yet. Interestingly, the proband and his daughter are

also heterozygous carriers of a rare (1.08% in the European population) PLG polymorphism (c.266G>A, p.Arg89Lys) while the daughter is heterozygous carrier of one more rare (1.11%) PLG polymorphism (c.1567C>T, p.Arg523Trp), both of unknown significance.

It would be very informative if Bork et al.¹ went back to their whole-exome sequencing data to investigate the possible co-segregation of gene variants encoding for other proteins of the contact system that may affect either the expression of the disease or its clinical phenotype. In support of this hypothesis is our finding that the F12-46C/T and the KLKB1-S143N functional variants are associated with the clinical severity of HAE due to C1-INH deficiency.^{4,5}

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The authors have no conflict of interest to disclose.

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