

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

To the Editor

In 1942, Urbach¹ described a case of chronic urticaria that was cured after surgical removal of a rectum carcinoma and suggested a causal relationship between chronic urticaria and malignancy. Since then, several cases of urticaria linked to malignancies have been reported (Table 1).

Malignancies are generally not considered to cause urticaria or to be a rare cause of urticaria.^{2,3} The 2017 Revision and Update of the EAACI/GA²LEN/EDF/WAO Guideline for the Definition, Classification, Diagnosis and Management of Urticaria⁴ states that there is not sufficient evidence for a causal correlation of urticaria with neoplastic diseases to support routine screening for malignancies in the diagnosis of underlying causes for urticaria.

Here, we present a case of recalcitrant chronic spontaneous urticaria (CSU) and symptomatic dermographism that preceded a Hodgkin lymphoma (HL) for months and showed increased disease activity upon initiation of chemotherapy to disappear completely once the HL was controlled. This is similar to 25 other cases in the literature (in online repository, see Methods, Case references, and detailed Case descriptions).

A 33 yo female with a personal and first-degree family atopic background was seen in April 2010 with urticaria of 2 weeks' duration, presenting with generalized, partly confluent wheals of 1-3 centimeter diameter. The hives appeared spontaneously and with rubbing (symptomatic dermographism), were unresponsive to triple-dose levocetirizine plus montelukast, and only improved temporarily with oral glucocorticosteroids (OCS). After a 3-week prednisone washout, several laboratory tests were performed (Table 2). The only abnormal finding was antibodies against double-stranded DNA (dsDNA). Three months later, the patient returned with nasal obstruction and mild hives; mometasone furoate nasal spray was added. Two weeks later, the hives and the nasal obstruction exacerbated and an enlarged conglomerate of left-sided cervical lymph nodes was palpable, confirmed with CT scan. A biopsy leads to the diagnosis of HL, nodular sclerosis. In January 2011, chemotherapy was started. Hours after the first 2 chemotherapy sessions, there was a moderate-severe exacerbation of the hives that lasted for days. However, after the third chemotherapy session, all hives disappeared for good. The patient has been in remission for 7 years, and the hives have not returned.

As of now, malignancies have been reported to cause urticaria in a total of 26 cases, including ours (Table 1). With a median age of 47 years (10-70 years), 16 of 24 patients were 35 years or older.

Most had chronic (probably spontaneous) urticaria (17 of 23, 77%; Table 1), 4 had acute, 1 aquagenic, and 1 cholinergic urticaria. In 1 patient, urticaria was unilateral. The urticaria was mostly reported as poorly responsive to conventional treatment; all described patients needed OCS to obtain intermittent relief. The majority (15/22) of patients had been suffering from urticaria for 2-8 months before the malignancy was detected.

The malignancies that were found to be linked to urticaria in the case reports were mainly carcinomas (17 of 25, 68%), with only 24% being of hematologic origin, 1 seminoma, and 1 astrocytoma. Twenty-four percent of all cases were papillary carcinomas of the thyroid gland.

In 19 of 25 cases, the malignancy was detected at an early, asymptomatic stage, because of a thorough workup by the treating physicians in search of a cause for the urticaria. After cure by chemotherapy or resection of the tumor, the urticaria in all patients resolved quickly, within days to a few weeks. All cured patients remained free of urticaria, with a postcure observation period from 4 months to 12 years. Some cases from more than 12 years ago died of cancer, though. The most remarkable cases strongly indicate a cause-effect relationship. In 4 cases (cases 6, 12, 14, and 25, Table 1), the urticaria showed initial resolution days after remission of the tumor, and a recurrence of the urticaria led the physicians to search for, detect, and treat the cancer relapses. The 2 most noteworthy cases were a 49-year-old female (case 26), who presented with a unilateral, resistant, left arm urticaria. A broad search for the cause identified a grade 1 left breast cancer; the urticaria resolved after total mastectomy. Urticaria recurred a year later, on the right arm: A 0.3 cm invasive tubular carcinoma of the right breast was detected. Urticaria finally disappeared after right mastectomy. The second case is ours, of generalized recalcitrant urticaria preceding HL. Urticaria flared up, during several days after the first 2 chemotherapy administrations, to disappear completely after the third.

To our knowledge, this is the first systematic collection of cases of CU very probably causally linked to malignancy.

Findings from previous studies partly support the notion that malignancies can cause urticaria: The relative risk of cancer among 12 720 Taiwanese patients with CU showed an increased standardized incidence ratio (SIR) of 2.2 (95% CI, 2.0-2.3), especially for hematologic malignant tumors (SIR = 4.1, 95% CI, 3.1-5.4) and non-Hodgkin lymphoma (SIR = 4.4, 95% CI, 3.0-6.1).⁵ In contrast, the Swedish cancer registry, in 1990, found cancer was less frequent in urticaria patients: 36 patients with urticaria had cancer (expected

TABLE 1 Case reports of cancer linked to urticaria

Author and year of publication	Type of urticaria (months before cancer was diagnosed)	Malignancy	Details ^a	Follow-up
1. Urbach (1942) ¹	70 yo male Urticaria	Rectum carcinoma	Removal of the tumor resulted in cure of the patient's hives.	NS
2-3. Sheldon (1955) ²	2 cases of urticaria (it seems tumor appeared first ^b)	Carcinoma of the Colon with central necrotic tissue.	Urticaria resolved after surgical removal of the primary tumor. No further information is provided.	NS
4. Hills (1968) ³	57 yo male Chronic urticaria (6 mo)	Non-mucin-secreting adenocarcinoma of the lung	Skin nodule biopsy showed anaplastic carcinoma. Patient also presented with carcinoid syndrome and weight loss. Patient died from complications, and autopsy revealed carcinomatous neuromyopathy.	NS
5. Anderson (1991) ⁴	68 yo male Chronic urticaria (12 mo)	Colon cancer	Surgical removal led to disappearance of all his skin problems.	NS
6. Reinhold (1996) ⁵	32 yo female Chronic urticaria (3 mo)	Metastatic ovarian carcinoma	After surgery and chemotherapy, urticaria cleared for 12 y. Reappearance of her urticaria led to diagnosis of peritoneal carcinomatosis. Second course of chemotherapy was ineffective and patient died.	12 y
7. Lipsker (1998) ⁶	46 yo male Chronic urticaria (5 y)	IgA myeloma	Patient had history of intermittent, antihistamine-resistant urticaria. Laboratory test only revealed an IgA monoclonal spike. Patient was referred to hematology. After first chemotherapy cycle, urticaria resolved, also IgA levels were low. Patient remained in complete remission 1y after bone marrow transplantation.	1 y after bone marrow transplantation
8. Mowad (1998) ⁷	37 yo male Urticaria (±8 wk)	Seminoma of the testes	Physical examination revealed a testicular mass. Surgical and radiation therapy led to gradual resolution of the urticaria with no recurrence.	±4 mo ^c
9. Clore (1999) ⁸	48 yo female Chronic cholinergic urticaria (4 y; uncontrolled for 3 mo)	Hairy cell leukemia	Patient presented with urticaria episodes precipitated by heat, stress, and effort. Blood count only revealed leucopenia. Three months after, laboratory studies showed pancytopenia. Upon initiation of chemotherapy, the pruritus and urticaria subsided.	NS
10. Alonso (2000) ⁹	59 yo male Chronic recurrent urticaria (during urticaria workup, leukemia becomes evident)	Chronic myelomonocytic leukemia	Patient had recurrent episodes of urticaria. Complete blood count showed monocytosis. When patient started chemotherapy, urticarial lesions healed successfully.	NS
11. Greiner (2002) ¹⁰	56 yo man Acute urticaria (diagnosis of carcinoma preceded urticaria by 2 wk)	Small cell carcinoma of the lung	Patient requires high-dose systemic steroids plus antihistamines for urticaria control. Following surgical removal of the tumor, the urticaria disappeared.	NS
12. Hill (2003) ¹¹	10 yo boy Chronic spontaneous urticaria (4 mo)	Acute lymphoblastic leukemia with eosinophilia	Patient presented with hypereosinophilia. Treatment with prednisone and hydroxyurea leads to decline in leukocyte count and skin lesions' resolution. After tapering, leukocyte count rose again and urticaria recurred. The patient's hypereosinophilia has persisted along with his urticaria.	Still leukemia and urticaria

(Continues)

TABLE 1 (Continued)

Author and year of publication	Type of urticaria (months before cancer was diagnosed)	Malignancy	Details ^a	Follow-up
13. Chien (2004) ¹³	10 yo female Urticaria (2 wk)	Acute lymphoblastic leukemia with eosinophilia	Laboratory examination revealed leukocytosis with hyper eosinophilia. Within days after initiating chemotherapy, patient's laboratories and symptoms improved.	NS
14. De P (2005) ¹⁴	57 yo male Chronic urticaria (4 y)	Large cell undifferentiated carcinoma of the lung	Resistant urticaria preceded cancer diagnosis. High-dose palliative radiotherapy relieved the patient from skin lesions. 12mo later, urticaria recurred and tumor relapse was detected. Chemotherapy controlled the tumor, and urticaria disappeared again. Also with a second tumor relapse, the urticaria came back. Second course chemotherapy leads to symptomatic improvement.	4 y, finally patient died
15. Shamsadini (2006) ¹⁵	12 yo female Chronic urticaria (3 mo)	Brain tumor: grade II astrocytoma	Recurrent urticaria with partial improvement with antihistamines. Three months after starting urticaria, lip fasciculation led to the diagnosis. 3y after a full course of radiotherapy, there was no recurrence of the tumor nor of the urticaria.	3 y
16-19. Manganoni (2007) ¹⁶	39 yo female Recalcitrant chronic urticaria ^d (3 mo)	Papillary carcinoma of the thyroid	Oral CS-resistant CSU. Euthyroid, without any clinical signs neck US, revealed a 10 mm cancer. Urticaria resolved completely 2 d after thyroidectomy.	6 y
	32 yo female Chronic generalized urticaria ^d (3 mo)	Papillary carcinoma of the thyroid	Oral CS-resistant CSU. Euthyroid, without any clinical signs neck US, revealed a 7 mm cancer. Urticaria resolved completely 4 d after thyroidectomy.	7 y
	61 yo female Chronic generalized urticaria ^d (2 mo)	Papillary carcinoma of the thyroid	Oral CS-resistant CSU. Euthyroid, without any clinical signs neck US, revealed a 9 mm cancer. Urticaria resolved completely 1 d after thyroidectomy.	5 y
	42 yo female Chronic generalized urticaria ^d (8 mo)	Papillary carcinoma of the thyroid	Oral CS-resistant CSU. Euthyroid, without any clinical signs neck US, revealed a 5 mm cancer. Urticaria resolved gradually 3 d after thyroidectomy.	NS
20. Özkaya, (2011) ¹⁷	25 yo female Aquagenic urticaria and syncope (6 mo)	Papillary carcinoma of the thyroid	Occult carcinoma, US detection. Resolved days after total thyroidectomy	6 mo
21. Baroni (2012) ¹⁸	63 yo male Chronic urticaria (6 mo)	Adenocarcinoma of the prostate	Urticaria nonresponsive to antihistamine and CS treatment. Urticaria workup: elevated prostate Ag. A few weeks after radical prostatectomy, the urticaria disappeared spontaneously.	2 y
22. Hu (2012) ¹⁹	60 yo female Chronic urticaria and angioedema (6 mo)	Bronchioloalveolar carcinoma with atypical adenomatous hyperplasia	Skin manifestations responded to loratadine. Attempts to stop treatment resulted in exacerbations. Carcinoma was detected 6 mo later on chest CT urticaria workup. 7 d after surgical treatment, antihistamines were suspended; the urticaria never recurred.	6 mo
23. Kartal (2012) ²⁰	25 yo male Acute urticaria (7 d)	Papillary carcinoma of the thyroid	Urticaria resistant to H1 antihistamines (2× dose) and oral CS. US detection of a 10 mm thyroid nodule. Disappearance of urticarial lesions 2nd day after thyroidectomy.	9 mo

(Continues)

TABLE 1 (Continued)

Author and year of publication	Type of urticaria (months before cancer was diagnosed)	Malignancy	Details ^a	Follow-up
24. O'Donnell ²¹	58 yo female Acute aggressive urticaria with angioedema (4 wk)	Breast cancer: Grade 1 invasive ductal carcinoma	Mastectomy with no further urticaria at the 4-wk control visit.	4 mo
25. Kasi (2016) ²²	49 yo female Unilateral arm urticaria (3 mo)	Multifocal grade 1 invasive breast cancer (left side) 12mo later: right side: Metachronous Bilateral Breast Cancer	The left-sided arm urticaria resolved after left mastectomy. 18 mo later: severe unilateral right arm urticaria. A grade 1 0.3 cm invasive tubular carcinoma was detected. Urticaria resolved completely after right mastectomy.	NS
26. Larenas-Linnemann (2017)	33 yo female Chronic spontaneous urticaria (8 mo)	Hodgkin lymphoma	Urticaria only controllable on oral CS. Cervical lymph node enlargement led to lymphoma diagnosis. Urticaria flared with the first 2 chemotherapy administrations. No further urticaria after 3rd course.	7 y

For references of the articles: see online repository at www.jaci.com

Ag, antigen; CS, corticosteroids; CSU, chronic spontaneous urticaria; CT, computerized tomography; mo, months; US, ultrasound; yo, years old

^aGray shading: the cancer was detected in an early stage with no signs, due to a thorough workup in the search of a cause for the urticaria.

^bThe author doubts if the psychologic stress of the diagnosis of colon carcinoma could have caused the urticaria, but the lesions disappeared after resection of the carcinoma.

^c15 fractions of radiotherapy.

^dby biopsy and immunoglobulin staining: no vasculitis. Thyroid auto-antibodies negative

number: 41). Malignancy appeared in the same year as urticaria or later in 23 (expected number 25.6).⁶

Of note, publication bias should be taken into account. One can assume that physicians will publish cases where CSU and cancer are linked, for example, because cancer treatment led to remission of CSU or because onset of CSU and cancer coincided. Also, cancer and CSU are common diseases and could co-occur in the same patient or go into remission together. However, the narrow time span between cancer remission and urticaria resolution and especially the recurrence of urticaria that led to detection of cancer relapse in some of our cases are arguments in favor of a causal relationship.

Unanswered questions remain. Does the comorbid cancer cause enough immunodysregulation to cause urticaria, even from the very first start of the malignancy in situ? Our patient presented false-positive anti-dsDNA antibodies, already previously linked to lymphoma.⁷ Or vice versa, could the altered immune response in severe chronic urticaria predispose to cancer? We could speculate on what this immune dysregulation might be, as a chronic inflammatory condition surrounding the in situ malignancy might lead to complement activation or an alteration in the coagulation pathways, both related to urticaria.⁸ Then, another issue to consider is as follows: Would patients have fared less well had cancer not been detected due to the urticaria workup? As there are many patients worldwide with CSU, we should be cautious to not overload the medical system and recommend a more in-depth workup in all CSU patients, to rule out these very rare cases of malignancy.

Our findings support the notion that CU and malignancies, in some patients, are linked. As in all CSU, complete blood count, C-reactive protein, and erythrocyte sedimentation rate should form part of the initial workup and would enhance detection of hematologic malignancies. In those over 45, age-indicated screening with mastography/prostate antigen test should be taken, and in very recalcitrant, treatment-resistant CSU, among others, a thyroid gland ultrasound could be considered to rule out the most frequently associated malignancies. More research is needed to explore the link between CU and malignancies and the underlying mechanisms.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

DLL prepared case report, reviewed cases in the literature, and wrote the manuscript. SSS contributed to suggestions on the literature search, personal discussion of the issues explained in text, and corrected several reiterative draft versions of the manuscript. AAAJ developed online repository with details of cases, search, and description of cases, completed the table, and corrected the manuscript. MM contributed to suggestions on the

TABLE 2 Laboratory tests and Laboratory tests and imaging of the here presented patient

June 10, 2010	dsDNA: 51.4 U/mL (nl. < 9.6) CBC including basophil count, ESR, blood chemistry including liver function, C3, C4, CH50, urinalysis, stool ova and parasites, food panel of specific IgE: all normal
September 9, 2010	dsDNA: 16.2 U/mL, mild lymphopenia (total count 1360/mL), rheumatoid factor negative, C3 and C4 normal, CRP-HS: 0.305 mg/dL
December 10, 2010	Left cervical mass palpable, seems a lymph node package Thyroid function testing normal
December 21, 2010	Cervical CAT scan, contrasted: unilateral, left-sided, cervical, and supraclavicular conglomerate of enlarged lymph nodes
January 26, 2011	Lymph node biopsy: Hodgkin lymphoma, nodular sclerosis Immunohistochemistry: CD20, CD3, CD15: negative; CD30: positive Bone marrow biopsy: no infiltration of neoplastic cells

CAT, computerized axial tomography; C, complement; CBC, complete blood count; CRP HR, C-reactive protein high sensitivity; dsDNA, double-string deoxyribonucleic acid; Ig, immunoglobulin.

literature search, cowriting of discussion, and corrected several reiterative draft versions of the manuscript.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

Online repository content

- 1) Methods
- 2) Hill's criteria for causation applied to the 26 here presented cases, supporting the hypothesis of a relationship based on causation between neoplasia and urticaria.
- 3) References from table 1
- 4) Case Abstracts: more detailed descriptions of the cases from table 1

1) Methods

We describe our case and conducted a literature search in PubMed and Embase with the Mesh terms [malignancy] OR [carcinoma] OR [cancer] AND [urticaria]. We selected publications in English, Spanish, French, German or Dutch. We further searched references from the publications found. Only reports of original cases or series were taken into account. Data were extracted into table 1 of the published article, with references in the online repository, as well as more detailed case abstracts.

2) Hill's criteria for causation neoplasia --> urticaria applied to the here presented cases

Hill's criteria for causation (1965) are still the most recognized ones in medicine to proof causation: Here below we explain how the here presented cancer → urticaria relationship can be evaluated based on the cases we present (ours and from literature):

1. **Strength** A relationship is more likely to be causal if the correlation coefficient is large and statistically significant.
-- does not apply, because we are only reporting cases, but absence/impossibility of evidence of correlation does not rule out causation. Hill states: 'There are quite some reasons for a lack of correlation.'
2. **Consistency**: A relationship is more likely to be causal if it can be replicated.
+ Cases 6, 12, 14 and 25 in which the recurrence of the cancer was 'announced' by the recurrence of the urticaria.
3. **Specificity**: A relationship is more likely to be causal if there is no other likely explanation.
+ Though the urticaria flare-ups during the first two cycles of chemotherapy might have been caused by the drugs, this would not explain the urticaria already present for months pre-diagnosis of the cancer.
4. **Temporality**: A relationship is more likely to be causal if the effect always occurs after the cause.
+ Even if this is clearly (and luckily) not true for all urticaria in general, it is true for those cases reported here with a relapse of the cancer. All relapses were accompanied by flare in the urticaria (in many of them, the urticaria-flare-up stimulated the treating physicians to look for cancer recurrence).
5. **Gradient**: A relationship is more likely to be causal if a greater exposure to the suspected cause leads to a greater effect.
+ Case 8: surgical resection, followed by chemotherapy led to gradual reduction and finally resolution of the urticaria with no recurrence at 4 months' follow-up
6. **Plausibility**: A relationship is more likely to be causal if there is a plausible mechanism between the cause and the effect.
+ There are several plausible mechanisms, but none proven: foreign body hypothesis = during cancer cell growth, non-self antigens are liberated, which might cause an allergic reaction to them. Complement-factor hypothesis = cancer growth activates complement. [Or there might even be an explanation vice-versa: aberrant functioning of the immune system secondary to aggressive urticaria reduces the surveillance function of the immune system, giving room to cancer cell growth.]
Different cases, can have different mechanisms.

7. **Coherence:** A relationship is more likely to be causal if it is compatible with related facts and theories.
8. ****** The causal relationship cancer → urticaria is **compatible** with the here presented facts of the 26 cases
9. **Experiment:** A relationship is more likely to be causal if it can be verified experimentally. ***--*** Ethically not possible... or might be tested out with lab-animals...
10. **Analogy:** A relationship is more likely to be causal if there are proven relationships between similar causes and effects. ***+*** Other chronic inflammatory responses in tissue (e.g. chronic infection) are well-known causes of urticaria.

3) References from table 1

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4) Case Abstracts: more detailed descriptions of the cases from table 1

Case 1. Chronic urticaria cured after the surgical removal of a rectum carcinoma.

Case 2 and 3. Two patients with carcinoma of the large bowel. In these two patients, common causes of urticaria were excluded. Skin lesions disappeared after removal of the primary carcinoma. No further information is provided.

Case 4. 57 year-old man with 18 month progressive weakness, 6-month urticaria, 3 month carcinoid syndrome and weight loss. Chest radiograph showed an enlargement of the upper left hilum. Biochemical studies showed a diabetic glucose tolerance curve (blood sugar at 2 hours 307mg per cent), blood urea 24mg/dl, sodium 141mEq/L, potassium 2.3mEq/L, bicarbonate 30mEq/L, chloride 91mEq/L, urinary 5-hydroxy-indolacetic acid increased. Biopsy of skin nodule showed anaplastic carcinoma. He became very weak and died with bronchopneumonia. Autopsy showed carcinoma surrounding and infiltrating the posterior segment of the upper lobe with metastases in both lungs, in the myocardium, liver, mesentery, kidneys, tail of pancreas and thyroid. Adrenals were large and almost replaced by tumour. The psoas muscle biopsy showed carcinomatous neuromyopathy.

Case 5. Article could not be obtained.

Case 6. 32 year-old female with 3-month urticaria. Oral antihistamine resulted in slight improvement. Addition of oral corticosteroid was ineffective. An extensive evaluation revealed the presence of a metastatic ovarian cancer. Patient underwent surgery and five cycles of chemotherapy, after which urticaria disappeared. After 12 years, patient presented an urticaria relapse associated with peritoneal carcinomatosis. Palliative chemotherapy was given but ineffective for ovarian cancer and urticaria.

Case 7. 46 year-old male with 5 year history of intermittent, antihistamine-resistant urticaria and 2 episodes of angio-oedema. Weals resolved within 12h. Blood count was normal, a slightly increased erythrocyte sedimentation rate of 25mm/h was documented when urticaria was diagnosed, which steadily increased during follow-up. C-reactive protein and complement levels were within normal. Serum protein immunoelectrophoresis showed an IgA monoclonal spike (33.7g/L). Bence-Jones proteinuria was present. Bone marrow examination revealed important plasmocytosis. An extended work-up excluded autoimmune or infectious diseases as causative agents. Electrolytes, renal, hepatic and thyroid function were normal. Patient was referred to Haematology for chemotherapy. Urticaria resolved after first cycle of high-dose cyclophosphamide when IgA gammopathy was below 12g/L.

Case 8. 37 year-old male with 6 week urticaria. Screening laboratory tests were normal (blood count, liver function, electrolytes and urinalysis), erythrocyte sedimentation rate was elevated (44mm/h). On physical examination, a 2 cm right testicular mass was detected. Scan revealed a solid, heterogeneous, hypervascular mass. Alpha-1-fetoprotein and beta-human chorionic gonadotropin levels were measured and were within normal. Computed tomographic scan of the chest and abdomen showed normal findings. Patient underwent right radical orchiectomy. Subsequently patient was sent for postoperative adjuvant radiation. Patient experienced gradual resolution of symptoms and had no recurrence.

Case 9. 48 year-old female with 3 year history of urticaria (seven episodes). Rash was precipitated by heat, stress and effort. Punch biopsy of skin revealed infiltration of T-lymphocytes, mononuclear cells, mast cells and few eosinophils. Laboratory evaluation revealed normal electrolytes, liver function and thyroid test. Complete blood count showed leucopenia (2300 cells/mm³), without thrombocytopenia or anemia. First generation antihistamines were tried and provided relief for a period of 9-months. 3-months later patient presented bright rectorrhagia. Examination revealed splenomegaly and lymphadenopathy, laboratory studies showed pancytopenia. Bone marrow biopsy showed irregular lymphocytes with tiny "hair-like" cytoplasmic projections, findings consistent with hairy cell leukemia. Patient underwent intensive chemotherapy with 2-chlorodeoxyadenosine, which induced leukemia remission. In addition, her urticaria and pruritus resolved.

Case 10. 59 year-old male with recurrent urticaria, anti-histamines failed to relieve his symptoms. Punch biopsy of skin lesion revealed perivascular infiltration of T-lymphocytes, mononuclear cells and few eosinophils. Laboratory evaluation revealed normal electrolytes, liver function test and thyroid function. IgE-mediated reactions, systemic illness and parasitic infestations were ruled out. Complete blood count showed monocytosis ($1.2 \times 10^9/L$). Bone marrow examination revealed 11% blast cells and 5% monocytes. Diagnosis of chronic myelomonocytic leukemia was established. When patient started chemotherapy clinical symptoms and urticaria disappeared.

Case 11. 56 year-old male with 5-day history of acute urticaria and angioedema with small cell carcinoma of the lung. Results of a comprehensive laboratory workup (complete blood count, liver enzymes, kidney function, electrolytes, antistreptolysin, thyroid function and antinuclear antibodies) did not show abnormalities, with the exception of an elevated C-reactive protein (20mg/dL). Patient require a combination of high-dose steroid with antihistamines for urticaria to fade. Following surgery for the carcinoma patient stayed free from urticaria.

Case 12. 10 year-old male with 4-month history of urticaria. One month prior to evaluation patient's skin lesions spontaneously resolved, with simultaneous onset of general malaise, headache, back pain and fever. Complete blood count showed a significant leukocytosis of $35 \times 10^9/L$ with an eosinophilic predominance of 60%. Metabolic examination, urinalysis, and erythrocyte sedimentation rate were normal, as complement and immunoglobulin levels. Toxocara titers, isohemagglutinin titers and stool sample were unremarkable. Chest radiograph, electrocardiogram, and echocardiogram were normal. Bone marrow biopsy and aspirate revealed 70% cellularity with a predominance of myeloid precursors (50-60% of the eosinophilic lineage). Mild megakaryocytic hyperplasia was also present. Skin eruption recurred, patient had widespread coalescing, annular, erythematous plaques with central clearing. Skin biopsy was taken. Histopathology showed a mild perivascular infiltrate of inflammatory cells, lymphocytes and eosinophils in the dermis accompanied by a few neutrophils and mast cells. Treatment with prednisone was initiated with resolution of skin lesions and decline of leukocyte count. After tapering his leukocyte count again began to rise and his skin eruption recurred. Patient was diagnosed with hypereosinophilic syndrome. Treatment with hydroxyurea was initiated with patient's condition stabilization for 7 months approximately. A repeat bone marrow biopsy due to worsening symptoms revealed 30% lymphoblasts and persistent eosinophilia. Patient's hypereosinophilia has persisted along with his urticarial skin eruption.

Case 13. 10 year-old female with 2-week history of urticaria. Patient also reported a recent loss of appetite. Laboratory examination revealed white blood cell (WBC) count of 30,000/uL with a differential of 22,500/uL eosinophils. Erythrocyte sedimentation rate was elevated at 19mm/h. Stool sample was positive for cysts of Giardia lamblia. Treatment for giardiasis resulted in resolution of her previous complaint of appetite loss. Patient's urticarial plaques, WBC and eosinophils remained unchanged. Patient was referred to the hematology clinic, where bone marrow biopsy confirmed a diagnosis of pre-B cell acute lymphoblastic leukemia. Within days after initiating chemotherapy WBC, eosinophils and rash began to resolve.

Case 14. 57 year-old with 4-year urticaria treated with antihistaminic, steroid ointments, emollients and oral corticosteroids without any benefit. Complete blood count, erythrocyte sedimentation rate, renal and liver function, anti-streptolysin O titers, C3, C4 and C1 esterase inhibitor levels were normal on repeating testing. Later he presented to casualty department with right-sided pleuritic

pain. Chest x-ray revealed right lower lobe collapse. CT scan of chest confirmed a soft tissue mass. Endobronchial histology confirmed a cell undifferentiated carcinoma of the lung. When treated by external be a high dose palliative radiotherapy (39 Gray in 13 fractions) with urticarial rash remission. One year after, rash returned and tumour recurrence was confirmed. Chemotherapy achieved tumour mass regression and rash disappearance. 10 months following he had similar cutaneous manifestation and spread of tumor was confirmed. A second course of chemotherapy helped symptomatic improvement. However, cerebral metastasis lead to patient's death.

Case 15. 12 year-old female with recurrent episodes of urticaria treated with partially effective antihistamines. 3-month later, she began to exhibit prominent fasciculation of her lower lip. A mass was identified adjacent to the cerebellum by CT scan. Fine-needle aspiration revealed a grade-II astrocytoma. Tumor was not operable, radiotherapy was begun; after first cycle, urticarial eruption and lip fasciculation ceased. Follow up 3-years after revealed no recurrence.

Case 16. 39 year-old female with 3-month urticaria which persisted despite oral antihistamine therapy associated with oral corticosteroid. Laboratory testing revealed no abnormalities in blood count, liver and kidney function, sedimentation rate, inflammatory indexes, complement fraction, and C1 esterase inhibitor levels. Antinuclear antibodies and thyroid antibodies were negative; thyroid function was normal. Biopsy of skin revealed no sign of vasculitis. Ultrasound of the neck revealed an hypo echoic area in the right lobe of the thyroid with foci of calcification. Fine-needle biopsy revealed the presence of a papillary carcinoma if the thyroid. After 2 days of total thyroidectomy, urticaria resolved and no other episodes recurred after 6 years.

Case 17. 32 year-old female with 12-week urticaria. Antihistaminic and steroid treatment yielded no improvement. Laboratory testing showed no abnormalities in blood count, liver, kidney and thyroid function, sedimentation rate, inflammatory indexes, complement fraction and C1 esterase inhibitor levels. Test for antinuclear antibodies and anti-thyroid antibodies were negative. Skin biopsy showed histological changes compatible with urticaria. Ultrasound examination of the neck revealed a 7 mm hypoechoic nodule in the right lobe of thyroid. Fine-needle aspiration biopsy revealed papillae thyroid carcinoma. Four days after total thyroidectomy, urticaria resolve. 7-years later, patient remained without urticaria relapses.

Case 18. 61 year-old female with 2-month urticaria treated with antihistamines and oral steroid therapy without remission. Laboratory tests were negative. Thyroid function was normal. Skin biopsy showed a normal epidermis, dermal edema, sparse perivascular and interstitial eosinophils, lymphocytes, neutrophils and mast cells. Ultrasound examination of the neck revealed a 9mm hypoechoic nodule in the left lobe of the thyroid. Fine-needle aspiration biopsy revealed a papillae thyroid carcinoma. Patient underwent total thyroidectomy. After 1 day urticaria resolved. Five years later the patient had no further urticarial lesions.

Case 19. 42 year-old female with 8-month urticaria. Antihistamine and steroid therapy yielded no improvement. Laboratory test were normal. Test for thyroid autoantibodies and thyroid function were within normal limits. Skin biopsy showed histological changes consistent with urticaria. Ultrasound examination of the neck showed 5mm hypoechoic nodule in the right lobe of the thyroid. Fine-needle aspiration biopsy showed an occult papillary carcinoma. Patient underwent total thyroidectomy; 3 days after removal urticaria gradually resolved with no other episode.

Case 20. 25 year-old female with 6-month urticaria. Bathing exceeding 20-30 minutes always resulted in syncope. Angioedema or respiratory symptoms did not occur. Washing dishes by hand induced local lesions. Laboratory workup were unremarkable. Focal and systemic infections and autoimmune and other systemic diseases were ruled out. Neurologic and cardiovascular investigations revealed no other causes of syncope. Challenge tests with hot, ice-cold, and room-temperature water led to urticaria within 20 minutes. Exposure to heated air from a hair dryer at 40°C for 2 minutes. Skin biopsy findings were consistent with urticaria. Combined treatments with antihistamines, narrow band UV-B, shortening the bathing time, and alkalization of bath water were partially effective. Thyroid ultrasonography revealed a 12mm isoechoic, solid nodule in the left lobe of the thyroid gland. Fine-needle aspiration biopsy findings were consistent with papillary carcino-

ma of the thyroid. Patient underwent total thyroidectomy. Treatment with medications was stopped, and patient remain free of lesions at 6-months follow-up.

Case 21. 63 year-old male with 6-month urticaria. Patient had no history or allergies and denied drug use. Laboratory findings (blood examination, complement, C1 inhibitor antigenic level, thyroid function test, anti-thyroid anti-antibodies, antinuclear antibodies, rheumatoid factor, serum immunoglobulins level, immune complexes, stool screening for blood, parasites and yeast, serum electrophoresis, anti-Helicobacter pylori antibodies, anti-streptolysin O titer, renal and liver function, total immunoglobulin E) were unremarkable. Further investigation revealed an increased prostate-specific antigen level. Multiple prostate biopsies revealed presence of a histologically confirmed prostate carcinoma. Patient underwent radical prostatectomy and urticaria disappeared. Two years following prostatectomy patient was symptom free.

Case 22. 60 year-old female with a 6-month urticaria treated with Loratadine which controlled urticaria temporarily. Attempts to stop antihistamine therapy resulted in exacerbation. After 4 months of treatment symptoms became worse with swelling of lips. The remainder clinical examination was normal. Full blood count, electrolytes and liver functions tests were unremarkable; IgE was mildly raised; there was no evidence of hypersensitivity to common inhalants, food allergens and latex; C3, C4, immunoglobulins (IgA, IgG, IgM) and drum tumor index were all normal. Computerized tomography scan of chest showed a ground glass opacity in the right middle lobe. Histology confirmed a bronchioloalveolar carcinoma with atypical adenomatous hyperplasia. A week after surgical treatment, she stopped medicine an rash never recurred after 6 months follow-up.

Case 23. 25 year-old male with 7-day urticaria without any identifiable cause. Antihistamines were started with no response even after doubling the dose. Oral steroid was added with any benefit. Laboratory investigations were normal except for high levels of thyroid autoantibodies (anti-thyroid peroxidase, 55UI/mL, and anti-thyroglobuline 300UI/mL). Thyroid ultrasonography detected a hypoechoic nodule. Cytological examination through fine-needle aspiration biopsy reported a thyroid papillary carcinoma. Patient underwent total thyroidectomy with spontaneous urticarial symptoms disappearance 2 days after surgery. Patient remain symptom free after 9-months follow up.

Case 24. 58 year-old 1-week urticaria. Her medical history included basal cell carcinoma of the left forearm, Grave's disease and osteoarthritis. Patient received oral steroid and antihistamines with minimal resolution. Skin biopsies of the right hand and left thigh yielded results consistent with urticaria showing dermal edema with mixed dermal and pannicular inflammation with abundant eosinophils. Laboratory studies (thyroid function, serum protein electrophoresis, complement, antinuclear antibody, autoimmune blistering disease studies, flow cytometry and Lyme disease serology) were normal. Urinalysis revealed hematuria, which prompted further workup with urine cytology and CT both showing normal results. Age-appropriate cancer screening revealed four lesions in left breast through mammography. Biopsies demonstrated grade 1 invasive ductal carcinoma. Patient underwent left breast mastectomy. After 4-weeks patient showed no evidence of rash recurrence. After 4-months patient remained clear.

Case 25. 49 year-old female with and abnormal mammogram (abnormal calcifications in the superior lateral and superior medial quadrants of the left breast) and 12-week unilateral left arm urticaria. Excisional left breast biopsy showed multifocal, grade 1 invasive lobular carcinoma. Patient underwent left skin-sparing mastectomy with immediate breast reconstruction and left axillary sentinel lymph node biopsy followed by left axillary lymph node dissection. Pathology demonstrated nodopositive disease and multifocal and multi-centric invasive lobular carcinoma grade II. Left-side arm urticaria resolved after resection of the breast cancer. Patient received adjuvant dose-dense chemotherapy, followed by radiotherapy. 1-year after patient presented again with severe unilateral arm urticaria. Re-imaging of the patient showed calcifications in the right breast. Biopsy showed atypical lobular hyperplasia. Due to her prior history, consensus was to proceed with risk-reducing nipple-sparing mastectomy and immediate reconstruction on the right side. Pathology showed multiple foci of atypical lobular hyperplasia and a single focus of grade I invasive tubular carcinoma. Urticaria again resolved completely and spontaneously after tumor resection.

331 Case 26. The case reported in the letter.