Advances in Radiation Oncology (2024) 9, 101433

advances in radiation oncology

www.advancesradonc.org

Teaching Case

Urticaria Heralding Breast Cancer: Case Report and Literature Review

Benjamin Royal-Preyra, M.D., FRCPC,* Melanie Boucher, B. Sc. Inf, and Isabelle Marsan, B. Sc. Inf

Department of Radiation Oncology, Regional University Affiliated Hospital Centre of Trois-RIvieres, University of Montreal, Montreal, Canada

Received 23 October 2023; accepted 15 December 2023

Introduction

Paraneoplastic syndromes are relatively rare and occur because of aberrant immune, endocrine, or metabolic stimulation by cancer cells[1] and cause symptoms due to the generation of autoantibodies, cytokines, hormones, or peptides rather than direct tumor infiltration or metastasis.[2-3] Paraneoplastic syndromes are estimated to affect up to 8% of patients with cancer.[3] Treatment of a paraneoplastic syndrome involves treating the underlying malignancy, which usually, but not always, leads to the resolution of a patient's symptoms.[4] Paraneoplastic manifestations of breast cancer, including hypercalcemia, Sweet syndrome, dermatomyositis, and granulocytosis, are reported in the literature.[5] Urticaria as a paraneoplastic syndrome of breast cancer has only been reported 3 times in the English literature.[5-7] This report describes the case of a 43-year-old woman presenting with a 3-year history of monoclonal antibody refractory chronic diffuse urticaria that preceded the diagnosis of, and only resolved after treatment of, a luminal A breast cancer with surgery and adjuvant radiation. A review of the published literature on urticaria in breast cancer patients is also presented and discussed. Clinicians should be aware that breast cancer can present with generalized urticaria refractory to medical management.

Paraneoplastic syndromes occur in approximately 8% to 20% of patients with cancer.[3] They are characterized by symptoms caused by tumor secretion of peptides, hormones, cytokines, or immune cross-reactivity between malignant and normal tissues[3] rather than direct tumor infiltration, metastasis,[2] or treatment-related toxicity.[8] A paraneoplastic syndrome can affect almost any organ system, including the endocrine, neurologic, dermatologic, rheumatologic, and hematologic systems among others.[9] Paraneoplastic syndromes have been reported in a wide variety of cancers, most notably small cell lung, breast, gynecologic, and hematologic cancers.[3] After neurologic paraneoplastic syndromes, cutaneous manifestations are the second most common group of paraneoplastic syndromes and include acanthosis nigricans maligna, pachydermatoglyphia, erythema gyratum repens, bazex paraneoplastic acrocheratosis, necrolytic migratory erythema, pemphigus, pityriasis rotunda, dermatomyositis, palmoplantar keratoderma, pyoderma gangrenosum, and Sweet syndrome among others.[10] There are case reports describing chronic urticaria preceding a diagnosis of malignancy in breast cancer,[5-7] non-small cell lung cancer,[11] neuroendocrine tumor,[12] colorectal rectal cancer,[13,14] prostate cancer,[15] and chronic lymphocytic leukemia.[16] Timely diagnosis and management of these syndromes is complicated because the onset of symptoms can precede or follow the diagnosis of cancer, and the intensity of symptoms does not always parallel the severity of the underlying cancer.[17] Management of paraneoplastic syndromes usually involves a combination of treating the underlying malignancy, immune suppression, and correction of electrolytes and hormone derangements.[3] These syndromes can cause

Sources of support: This work had no specific funding. Research data are stored in an institutional repository and will be shared uponrequest to the corresponding author.

*Corresponding author: Benjamin Royal-Preyra; Email: benpreyra@gmail.com

https://doi.org/10.1016/j.adro.2023.101433

substantial morbidity[18] and early identification and treatment is critical to reducing their effect on patients.

Urticaria is a common dermatologic condition characterized by well-circumscribed raised cutaneous lesions ranging in size from several millimeters to several centimeters or larger and has a lifetime prevalence of approximately 20%.[19] It is immune-mediated and caused by the release of histamine and other inflammatory mediators from mast cells and basophils.[19] Various causes have been described in the literature, including physical contact, vascular, infectious, psychological, idiopathic, malignant, hematologic, medication related, aberrant immune system signaling, venomous, and food-related among others.[19,20] Chronic urticaria is defined as urticaria occurring at least twice a week for 6 weeks,[21] is idiopathic in 80% to 90% of cases,[19] and occurs in approximately 1% of the general population.[22] Treatment generally includes avoidance of triggers, first and second generation antihistamines, leukotriene receptor antagonists, corticosteroids, and, for refractory cases, treatment with immune-modulating agents, including omalizumab or cyclosporine.[19-21] Spontaneous remission occurs in approximately 50% of patients at 3 years, but patients often experience recurrent episodes throughout their lives.[21]

Chronic urticaria as a paraneoplastic syndrome preceding a cancer diagnosis has been reported for various malignancies, including breast,[5-7] non-small cell lung,[11] neuroendocrine,[12] colorectal,[13,14] prostate,[15] and chronic lymphocytic leukemia.[16] There is also some evidence that chronic urticaria seems to predispose patients to cancer,[16] although other authors dispute this.[17] This could suggest a common immunologic pathway involved in cancer and urticaria development. A proposed mechanism linking malignancy and urticaria is not defined in the literature but is presumably due to aberrant activation of mast cells, basophils, and eosinophils by the cancer.[22] The Urticaria Activity Score (called UAS 7 when used for 7 consecutive days) is a common scoring system used to grade the severity of chronic urticaria. A more detailed description of the scoring system can be found in the references.[23] Currently, only 3 published case reports in the English literature describe chronic urticaria as a breast cancer-related paraneoplastic syndrome.[5-7] This case report highlights the presentation, clinical course, and outcome of a woman presenting with chronic urticaria related to breast cancer.

Patient Information

Ms C is a 43-year-old, premenopausal, Caucasian woman with a past medical history significant for psoriasis, osteoarthritis, eczema, recurrent urinary tract infections, tubal ligation, and gastroesophageal reflux disease. Her medications include Tylenol, pantoprazole, and vitamin D. She does not have any known drug allergies. Her family history is significant for a mother with ulcerative colitis and a maternal grandmother with Crohn disease.

In January 2019, she developed itchy raised skin lesions over her face, neck, arms, hands, chest, back, legs, and feet. The skin lesions were associated with severe pruritis, a sensation of heat, and pain that she described as pinching. She also reported cognitive changes with anxiety and decreased concentration secondary to these lesions. After the cutaneous lesions failed to resolve spontaneously, she sought medical attention from a local general medical clinic on April 12, 2019. Her vital signs were within normal limits, and she appeared clinically well. Physical examination revealed diffuse pruritic raised cutaneous lesions involving the face, neck, upper extremities, chest, back, legs, and feet (Figs. 1-3).

She was initially diagnosed with an exacerbation of her eczema and treated with Benadryl 50 mg by mouth taken four times daily as needed and Zantac 150 mg by mouth twice a day without an improvement in her symptoms. She was prescribed 40 mg of oral prednisone for 2 weeks which led some improvement of her symptoms. The prednisone was then tapered, and her symptoms quickly recurred after the dose of prednisone was decreased to 15 mg daily. At a follow-up visit on May 14, 2019, she reported persistent pruritic skin lesions and treatment was changed to Atarax 25 mg by mouth daily, Montelukast 10 mg by mouth daily, up dosed Cetirizine 10 mg 4 times daily by mouth, and Blexten 20 mg by mouth daily. Her UAS 7 was 35 per week. Atarax was stopped in September 2019 due to fatigue.

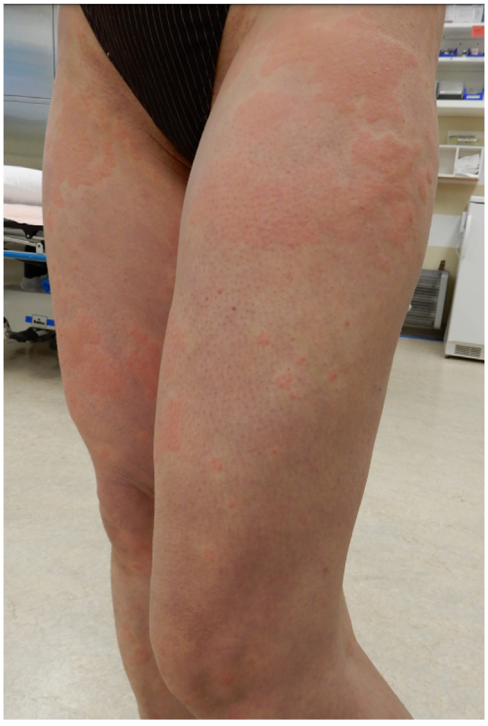

Figure 1 Anterior lower extremities.

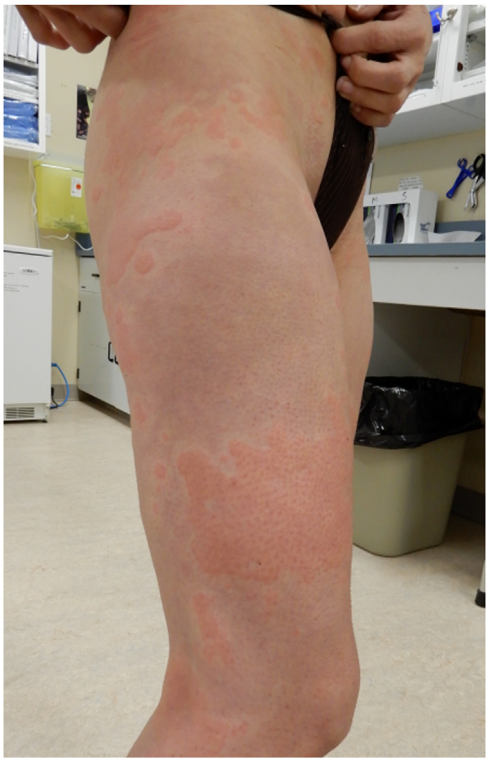

Figure 2 Lateral lower extremity.

On November 27, 2019, the patient was seen by dermatology where workup revealed normal complete blood count, creatinine, complement C3-4, and c-reactive protein. Antinuclear antibody 1:160 was positive. Biopsy of one of the cutaneous lesions was consistent with giant cell urticaria. Rupall 20 mg by mouth daily was added and Atarax was restarted because of persistent symptoms.

During the course of the next year, the patient was treated with Blexten, Rupall, Montelukast, Atarax, and Cetirizine with persistent urticaria. During this, her UAS score elevated, but stable, at around 29 to 30 weeks. On December 4, 2020, Reactine 40 mg by mouth daily was added with mild improvement in her symptoms but was later discontinued in September 2019 because of fatigue. In October 2021, Cyclosporin 2.5 mg/kg/d was added without benefit (UAS score remained 29-30/wk) and was discontinued at follow-up 1 month later. At that visit, Reactine 40 mg was restarted and Atarax and Blexten were stopped.

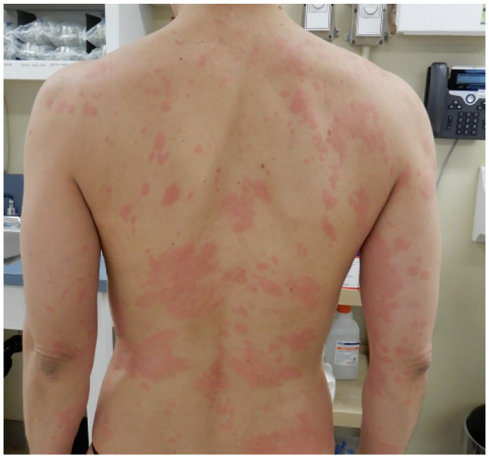

Figure 3 Back.

On November 16, 2021, the patient began treatment with Xolair 300 mg injections every 4 weeks with complete resolution of her urticaria within 24 hours (UAS7 score 0). Plaquenil was also added. At follow-up on April 1, 2022, the patient remained in complete remission (UAS score 0). However, at the next follow-up visit on May 20, 2022, the patient was found to have an early recurrence of her urticaria on her hands and feet with an UAS score of 30/wk. The patient also reported worsening diffuse arthralgias and dry hair at that time. She continued treatment with Xolair and Plaquenil.

In May 2022, the patient noticed a mass in her left breast. She sought medical attention on August 6, 2022, from her general practitioner and physical examination revealed a 2.5 cm mass in the superior midline of the left breast. At that visit, she was also found to have persistent urticaria with an UAS score of 30/wk. Workup with bilateral breast ultrasound and mammography (September 1, 2022) revealed a 11 × 16 × 19 mm asymmetrical lesion in the upper outer left breast (BIRADS-4). No other breast lesions or concerning lymphadenopathy were seen. Biopsy of the left breast lesion was positive for invasive ductal carcinoma, grade 1, ductal carcinoma in situ present, estrogen receptors 99% positive, progesterone receptors 90% positive, human epidermal growth factor receptor-2 (HER2) negative, Ki-67 5%. At follow-up with her general practitioner on October 11, 2022, her urticaria was found to be progressing despite Xolair and Plaquenil. Xolair and Plaquenil were stopped given the lack of benefit and upcoming breast surgery.

On October 15, 2022, the patient was managed with left breast partial mastectomy and sentinel lymph node biopsy. Surgical pathology revealed a 1.8 cm invasive ductal carcinoma, grade 1, 0/2 sentinel lymph nodes involved, estrogen and progesterone receptors strongly positive, HER2 negative. All surgical margins were negative. Oncotype DX was ordered (RS 10) and no adjuvant chemotherapy was given. The patient was initially seen by radiation oncology in consultation on December 5, 2022, and reported a complete resolution of her urticaria despite no active antiurticaria treatment. She was treated with adjuvant left whole breast radiation therapy 26 Gy/5 fractions + 10 Gy/5 fraction boost. She decided not to take adjuvant hormone therapy.

At our last follow-up on October 14, 2023, there was no clinical evidence of recurrent breast cancer or recurrent urticaria despite no active urticaria treatment for the 1 year.

Discussion

Cutaneous paraneoplastic syndromes associated with breast cancer in the literature include dermatomyositis (25%-50% of cases paraneoplastic), multicentric reticulohistiocytosis (25% of cases paraneoplastic), erythema gyratum repens (82% paraneoplastic), Sweet syndrome (20% of cases paraneoplastic), malignant acanthosis nigricans, hypertrichosis lanuginose acquisita, acquired ichthyosis, and extramammary Paget disease.[24,25] Other paraneoplastic syndromes associated with breast cancer reported in the literature include granulocytosis, opsoclonus myoclonus, cerebellar degeneration, retinopathy, lower motor neuron disease, Stiff man syndrome, sensory neuropathy, encephalitis, hypercalcemia, and urticaria.[3,6,7,26-28]

To date, only 3 case reports in the literature describe urticaria as a paraneoplastic syndrome of breast cancer.[5-7] The first case reported in the literature[7] is that of a 56-year-old woman who presented to medical attention after 7 months of generalized urticaria. She was known for recurrent basal cell carcinomas, genital herpes, renal agenesis, hypertension, and tachycardia. Her symptoms failed to resolve with antihistamines and oral corticosteroids. Further workup with complete blood count, hepatic function, renal function, inflammatory markers, chest x-ray, and urinalysis were normal. Screening with PAP smear was normal, but mammography and ultrasound revealed a right breast lesion that was biopsied and positive for invasive mucinous carcinoma, grade 1, and ductal carcinoma in situ, estrogen receptor-positive, progesterone receptor-negative, and HER2neu negative. She was treated with surgical resection, and her urticaria resolved within 2 days. Follow-up 4 months later revealed no recurrent urticaria despite no antihistamine or corticosteroid use. The second case reported[6] in the literature is of a 58-year-old woman who presented with a 1-week history of urticaria on her palms that failed to resolve with topical steroids and antihistamines. Her medical history included cutaneous basal cell carcinoma, Graves' disease, and osteoarthritis. Her symptoms gradually progressed during the following weeks to extend to her entire arms, abdomen, pubic area, buttocks, and face. She was treated with systemic steroids, which led to a partial improvement in her symptoms. Biopsy of one of the cutaneous lesions was consistent with urticaria. A thorough workup with thyroid function, antinuclear antibodies, serum protein electrophoresis, Lyme disease serology, urine cytology, and CT urogram, and pap smear were normal. She ultimately had a mammography that revealed 4 left breast lesions that were biopsied and positive for grade 1 invasive ductal carcinoma, estrogen and progesterone receptor-positive, HER2neu negative. She was treated with a left breast mastectomy and was tapered off systemic corticosteroids. One-month postsurgery, she had no evidence of urticaria and remained urticaria-free at follow-up 4 months later. The third case reported in the literature[5] is that of a 49-year-old woman without any medical history who presented with an abnormal screening mammography showing left breast calcifications. She also reported a 3-month history of lateral arm urticaria. She was not known for urticaria or any other dermatologic conditions previously. Excisional left breast biopsy showed multifocal invasive lobular carcinoma, grade 1. She was treated with a left breast mastectomy and sentinel lymph node biopsy. The sentinel lymph node was positive, and she went on to have a left axillary lymph node dissection. The final pathology showed multifocal and multicentric invasive lobular carcinoma, T2, grade 2, 2/28 lymph nodes positive, N1, margins negative, estrogen and progesterone receptor-positive, Her2neu negative. Her left arm urticaria improved immediately after surgical resection. She received adjuvant dose-dense Adriamycin, cyclophosphamide, and paclitaxel, adjuvant locoregional radiation therapy, and adjuvant hormonotherapy. Twenty-three months later, she presented with recurrent severe right arm urticaria and a workup with mammography revealed right breast microcalcifications that were biopsied and positive for atypical lobular hyperplasia. Given her history, she opted to undergo right breast mastectomy with surgical pathology confirming positive for invasive tubular carcinoma, grade 1, pT1aNx, estrogen and progesterone receptor positive, HER2 negative. Her right arm urticaria again resolved immediately after surgery and she resumed hormone therapy.

The available published literature that describes how to determine causality between a paraneoplastic syndrome and underlying cancer is mainly limited to neurologic diseases where a classic paraneoplastic syndrome is associated with a typical underlying neurologic disease, and the underlying causal antibody is known.[29,30] We were unable to find any publications describing criteria to determine causality between cutaneous paraneoplastic syndromes and underlying cancer. The World Health Organization-Uppsala Monitoring Center has published a standardized case causality assessment scale.[31] This system was originally designed to determine whether causality exists between medications/vaccines and adverse reactions, but many of the principles apply to determining causality between a disease and symptoms (Fig. 4). The link between this patient's urticaria and breast cancer likely falls somewhere between the probably/likely and possible categories. The patient's urticaria (the event) has a plausible time relationship with the disease, the response (cessation of urticaria symptoms) to withdrawal (breast surgery) is clinically reasonable and rechallenge is not required (no recurrence of urticaria after surgery). The only criterion that does not fit in the probable/likely category is that the symptom is

Table 2. WHO-UMC Causality Categories

Causality term	*Assessment criteria**
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable / Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Conditional / Unclassified	• Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable / Unclassifiable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

* All points should be reasonably complied with

Figure 4 World Health Organization Uppsala Monitoring Centre-Causality Assessment Criteria.

unlikely attributable to another disease (we cannot be confident of this given the prevalence of urticaria in the general population). The temporal relation between the cessation of the patient's urticaria symptoms during the month after breast surgery is the strongest factor that points to a causal relationship.

In all 3 cases reported in the literature,[5-7] the diagnosis of urticaria preceded the cancer diagnosis by several weeks, failed to respond to standard urticaria-directed treatment such as corticosteroids or monoclonal antibodies, and improved after surgical resection of the underlying malignancy. In one of these cases, recurrent urticaria also preceded contralateral breast cancer recurrence and again resolved spontaneously after the tumor was resected.[5] Although this anecdotally suggests a relationship between breast cancer and urticaria, a large epidemiologic study examining the link between urticaria and malignancy in 1155 patients found no association.[17] Given the high prevalence of both urticaria and breast cancer in the general population, the possibility of the 2 appearing concurrently due to chance alone is difficult to exclude. Based on the currently available evidence, screening for malignancy in patients presenting with urticaria beyond normal age-appropriate screening cannot be recommended.[5] Still, clinicians should be aware that cancer can present as medically refractory urticaria.

Conclusion

Chronic urticaria is a paraneoplastic syndrome that is uncommonly associated with breast cancer.[5-7] The correct identification of this condition presents a challenge to clinicians because the onset of symptoms can precede or follow the cancer diagnosis, and there is no consistent link between the intensity of symptoms and the stage or grade of the underlying malignancy.[17] All 3 patients with breast cancer and urticaria reported in the English literature had complete spontaneous resolution of their symptoms with surgical resection of their breast cancer, and recurrent urticaria preceded a recurrent breast cancer diagnosis in one patient. Given the high prevalence of both breast cancer and urticaria in the general population and the lack of a consistent epidemiologic relationship between the 2 in the literature, screening for malignancy in patients presenting with urticaria beyond normal age-appropriate screening is not justified at this time. Additional research is needed to characterize the relationship between these 2 conditions better.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could

have appeared to influence the work reported in this paper.

References

1. National Institute of Neurologic Disorders and Stroke. Paraneoplastic syndromes. Accessed August 1, 2023. https://www.ninds.nih.gov/health-information/disorders/paraneoplastic-syndromes.
2. Thapa B, Mahendraker N, Ramphul K. Paraneoplastic syndromes. *StatPearls*. StatPearls Publishing; 2022.
3. Pelosof LC, Gerber DE. Paraneoplastic syndromes: An approach to diagnosis and treatment. *Mayo Clin Proc*. 2010;85:838-854.
4. Pelosof LC, Gerber DE. Paraneoplastic syndromes: An approach to diagnosis and treatment. *Mayo Clin Proc*. 2010;85:838-854. (Erratum in: *Mayo Clin Proc*. 2011;86:364. Dosage error in article text).
5. Kasi PM, Hieken TJ, Haddad TC. Unilateral arm urticaria presenting as a paraneoplastic manifestation of metachronous bilateral breast cancer. *Case Rep Oncol*. 2016;9:33-38.
6. O'Donnell E, Havyer R. Breast malignancy masquerading under the cloak of acute urticaria. *BMJ Case Rep*. 2014;2014: bcr2013202494.
7. Daniel BS, Murrell DF. Chronic urticaria resolving after resection of mucinous breast cancer. *J Clin Exp Dermatol Res*. 2010:1.
8. El Rassy E, Assi T, Kattan J, Pavlidis N. Paraneoplastic syndromes in cancers of unknown primary: An unknown field for oncologists. *Bull Cancer*. 2019;106:590-603.
9. Stolinsky DC. Paraneoplastic syndromes. *West J Med*. 1980;132:189-208.
10. Maurer M, Rosén K, Hsieh HJ, et al. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. *N Engl J Med*. 2013;368:924-935.
11. Ceasovschih A, Voloc G, Șorodoc V, et al. From chronic pruritus to neuroendocrine tumor: A case report. *Exp Ther Med*. 2022;23:189.
12. Pitchford CA, R Shenk ME, Zurowski S, Smith EH. Paraneoplastic erythema annulare centrifugum eruption (PEACE) associated with metastatic colorectal adenocarcinoma. *Cureus*. 2021;13:e18443.
13. Gibb J, Babawale O, Phan YC, Karim O. Dermatological manifestation of metastatic prostate cancer. *BMJ Case Rep*. 2020;13: e237115.
14. Younis AA. Urticarial vasculitis as an initial manifestation of colonic carcinoma: A case report and review of the literature. *Reumatismo*. 2018;70:259-263.
15. Kassim JM, Igali L, Levell NJ. A 14-year paraneoplastic rash: Urticarial vasculitis and dermal binding bullous pemphigoid secondary to chronic lymphocytic leukaemia. *Clin Exp Dermatol*. 2015;40:391-394.
16. Chen YJ, Wu CY, Shen JL, Chen TT, Chang YT. Cancer risk in patients with chronic urticaria: A population-based cohort study. *Arch Dermatol*. 2012;148:103-108.
17. Fanous I, Dillon P. Paraneoplastic neurological complications of breast cancer. *Exp Hematol Oncol*. 2016;5:29.
18. Schaefer P. Acute and chronic urticaria: Evaluation and treatment. *Am Fam Physician*. 2017;95:717-724.
19. Sachdeva S, Gupta V, Amin SS, Tahseen M. Chronic urticaria. *Indian J Dermatol*. 2011;56:622-628.
20. Grattan CE, Sabroe RA, Greaves MW. Chronic urticaria. *J Am Acad Dermatol*. 2002;46:645-657. quiz 657-660.
21. Jiménez LF, Castellón EA, Marenco JD, et al. Chronic urticaria associated with lung adenocarcinoma—A paraneoplastic manifestation: A case report and literature review. *World J Clin Cases*. 2022;10:7553-7564.
22. Kolkhir P, Altrichter S, Munoz M, Hawro T, Maurer M. New treatments for chronic urticaria. *Ann Allergy Asthma Immunol*. 2020 Jan;124:2-12. (Erratum in: *Ann Allergy Asthma Immunol*. 2022;128:234).
23. Hawro T, Ohanyan T, Schoepke N, et al. The Urticaria Activity Score: Validity, reliability, and responsiveness. *J Allergy Clin Immunol Pract*. 2018;6:1185-1190.e1.
24. Levine D, Miller S, Al-Dawsari N, Barak O, Gottlieb AB. Paraneoplastic dermatoses associated with gynecologic and breast malignancies. *Obstet Gynecol Surv*. 2010;65:455-461.
25. Tan AR. Cutaneous manifestations of breast cancer. *Semin Oncol*. 2016;43:331-334.
26. Rees JH. Paraneoplastic syndromes: When to suspect, how to confirm, and how to manage. *J Neurol Neurosurg Psychiatry*. 2004;75:ii43-ii50.
27. Grunbaum A, Kremer R. Parathyroid hormone-related protein (PTHrP) and malignancy. *Vitam Horm*. 2022;120:133-177.
28. Shah S, Flanagan EP, Pritikanta P, et al. Population-based epidemiology study of paraneoplastic neurologic syndromes. *Neurol Neuroimmunol Neuroinflamm*. 2021;9:e1124.
29. Graus F, Vogrig A, Muñiz-Castrillo S, et al. Updated diagnostic criteria for paraneoplastic neurologic syndromes. *Neurol Neuroimmunol Neuroinflamm*. 2021;8:e1014.
30. Binks S, Uy C, Honnorat J, Irani SR. Paraneoplastic neurological syndromes: A practical approach to diagnosis and management. *Pract Neurol*. 2022;22:19-31.
31. The Uppsala Monitoring Centre. The used of the WHO-UMC system for standardized case causality assessment. Accessed August 1, 2023. https://www.who.int/docs/default-source/medicines/pharmacovigilance/whocausality-assessment.pdf.