ORIGINAL RESEARCH

Diagnostic Approach to Patients with Chronic Pruritus of Unknown Origin: A Single-Site Retrospective Chart Review

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ABSTRACT

Background: Patients with generalized pruritus lacking primary skin lesions are typically subjected to extensive laboratory tests. For many, the results fail to reveal any clinically significant findings; the British Association of Dermatologists published detailed guidelines for the work-up and management of these patients. Our objectives were twofold: to evaluate the clinical utility of the diagnostic approach used in our practice, and to ascertain how closely we adhered to the suggested guidelines.
Methods: We conducted a retrospective chart review of 106 adult patients who presented with generalized pruritus without primary skin lesions.
Results: While 82.1% of patients received at least a complete blood count, far fewer received serum ferritin (23.6%) or chest imaging (36.8%). Almost 11% of patients responded to empiric anti-scabetic treatment. Approximately 9% of the skin biopsies were consistent with bullous pemphigoid. One patient had resolution of their pruritus after discontinuing an angiotensin-converting-enzyme inhibitor.
Conclusion: In conclusion, dermatologists should consider empiric anti-scabetic treatment, skin biopsies for patients over the age of 65, and discontinuation of an angiotensin-converting-enzyme inhibitor enzyme.

INTRODUCTION

Pruritus is one of the most common symptoms in dermatology, [1] especially in elderly patients. [2] Chronic pruritus (defined as itching for at least 6 weeks) is estimated to have a prevalence of almost 17% in adults [3] but likely greater than 50% patients over the age of 65. [4] Chronic pruritus is associated with a "markedly reduced quality of life" [5] that is not to be underestimated. In fact, living with chronic itch is comparable to living with chronic pain. [6] Hemodialysis patients with moderate to severe pruritus were more likely to feel drained, have poor sleep quality, and to have physician-diagnosed depression. [7] Pruritus in psoriasis patients is associated with agitation, depression, difficulty concentrating, and anxiety. [8]

Generalized pruritus without any primary skin lesions can be due to underlying systemic disorders or deemed idiopathic. [9] Various terms have been used to describe these patients, including chronic idiopathic pruritus, chronic pruritus of unknown origin, [10] generalized pruritus of unknown origin, [9] and Willian's itch. [11] Recently, Kim et al. recommended the use of the term Chronic Pruritus of Unknown Origin (CPUO) as it would encompass the diverse array of patients with chronic itch. [10] In 2018, the British Association of Dermatologists (BAD) published guidelines detailing the

recommended work-up (and treatment) of CPUO, which is as follows: Detailed history, detailed examination, ferritin, full blood count, urea and electrolytes, liver function tests, erythrocyte sedimentation rate (or C-reactive protein if unavailable), and chest x-ray. [9] The guidelines specifically state that patients "should *not* undergo routine endocrine investigations (including thyroid function tests) unless they present with additional clinical features suggesting diabetes, other endocrinopathy or renal disease." [9] Recently, Patel et al. recommended a skin biopsy for such patients as the presence of peripheral or tissue eosinophilia can help guide treatment strategies. [12] The purpose of our study was to evaluate the clinical utility of the diagnostic approach used in our practice for patients who presented with generalized pruritus lacking primary skin lesions. Of note, while most patients were *not* ultimately diagnosed with CPUO, we would like to demonstrate that empiric treatment for scabies and performing biopsies to rule out bullous pemphigoid are worth considering in the diagnostic work-up.

METHODS

IRB approval was obtained for this study. Patients with pruritus were identified using the following ICD-10 billing codes: L29.9 (Pruritus, Unspecified), L28.2 (Other prurigo), L28.1 (prurigo nodularis) from December 2016 until August 2018. Patients were excluded if they had primary skin lesions, a diagnosis of atopic dermatitis at presentation to the authors, if they were pregnant, or if they were younger than 18 years of age. Patients with recent diagnoses of scabies or arthropod infection (within 6 months) were also excluded. Inclusion criteria included patients with generalized pruritus of at least 6 weeks duration. Generalized was defined as pruritus affecting at least 5 body parts (eg: 2 arms, 2 legs, and head) or the patient reporting that the pruritus was of a generalized nature. Patients with xerosis were included if they failed at least a 2-week trial of topical corticosteroids and emollients. Patients with prurigo nodularis were included if patients reported pruritus and if the lesions affected at least 5 body parts. Patients with generalized prurigo nodularis that were asymptomatic were not included in the study.

RESULTS

576 patient charts were identified using the billing codes above, of which 106 met our inclusion and exclusion criteria. There were 54 men and 52 women, with an average age of 68.4 years for males and 67.13 years for females. The duration of pruritus ranged from 6.5 weeks to greater than 18 years. 75 of the patients presented with either xerosis or generalized excoriations, while 31 patients had erythematous papules with or without excoriations, consistent with prurigo nodularis.

Table 1 summarizes the percentage of patients that received the minimum work-up recommended the British Association of Dermatologists. Bloodwork was either ordered, documented as reviewed by the dermatologist, or documented as being done by an outside provider, for 92/106 patients (86.8%). With regards to four of these 92 patients, it was documented that laboratory tests were reviewed, but we do not know which exact labs were ordered. One of the 92 patients was supposed to fax over results but the results were not visible in the chart. Thus, we were able to confirm a complete blood count (CBC) was performed in a total of 87/106 patients, of which all had a CBC

with differential except for two patients. 85/106 had serum urea, 79/106 had liver function tests, 25/106 had serum ferritin, and 39/106 had either a chest x-ray or chest computed-tomography (CT) done within the past 12 months prior to the visit for pruritus.

In our dermatology practice, aside from obtaining bloodwork, patients commonly received empiric treatment for scabies. As demonstrated in Table 2, a total of 55/106 patients were treated with either topical permethrin and/or oral ivermectin. 6/55 patients (10.9%) returned for follow-up visits with documented resolution of the pruritus. We then analyzed how many patients had received skin biopsies before or after presentation to the authors. The objective of the biopsies was primarily to rule out bullous pemphigoid (BP) or help confirm a diagnosis of prurigo nodularis. 28 patients received a biopsy for Hematoxylin and Eosin (H&E) as well as direct immunofluorescence (DIF), whereas 24 patients only had one biopsy for H&E. 5/54 patients who received skin biopsies had findings that could be consistent with bullous pemphigoid. Of note, medication switches were documented in 8/106 patients and 1/8 patients had resolution of their pruritus after switching an angiotensin-converting-enzyme inhibitor (ACEI) to an angiotensin-receptor-blocker (ARB).

Table 3 compares the work-up for patients who presented with prurigo nodularis compared to patients that did not have any skin lesions. In our study, the percentage of patients who received at least a CBC was similar in the patients with and without prurigo nodularis (80.7% vs 81.3%). In contrast, a higher percentage of prurigo nodularis patients were treated empirically for scabies (61.3% vs 49.3). Yet, 4/6 patients with confirmed scabies did not present with prurigo nodularis. Furthermore, a higher percentage of prurigo nodularis patients had skin biopsies performed (58.1% vs 44.0%), yet none of the five patients who were ultimately diagnosed with BP had presented with prurigo nodularis.

DISCUSSION

In summary, Table 4 demonstrates our approach. For the initial set of bloodwork, only CBC and CMP are ordered, with further tests done as needed. The use of serum ferritin is somewhat questionable as patients with iron deficiency anemia can have falsely elevated ferritin levels as it is an acute phase reactant. [9] In addition, if iron deficiency is suspected despite normal ferritin levels, the guidelines recommend ordering additional iron panel labs such as serum iron and total iron binding capacity. [9] With regards to chest imaging, chronic pruritus has a known association with malignancy, especially leukemia and lymphoma, and can occasionally precede the diagnosis by years. [13] Although we did not observe any patients with lymphoma in our study, we were limited by the duration of follow-up, and therefore we do routinely order chest x-rays. Medication history must be carefully reviewed as many drugs have been associated with pruritus. [4] Although only one patient in our study had resolution of their pruritus after lisinopril was discontinued, there have been several over the years in our practice.

We believe that an empiric trial of anti-scabetic treatment, both safe and inexpensive, is warranted in almost every patient. Patients may need more than one treatment of permethrin and may require oral ivermectin. As demonstrated in Table 2,

Table 1. Laboratory and imaging recommended by the British Association of Dermatologists

	CBC	Urea and electrolytes	Liver function tests	Ferritin	ESR or CRP	CXR or Chest CT
Number of Patients (%)	87/106 (82.1%)	85/106 (80.2%)	79/106 (74.5%)	25/106 (23.6%)	25/106 (23.6%)	39/106 (36.8%)

CBC: complete blood count; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; CXR: chest x-ray; CT: computed-tomography

Table 2. Clinical utility of approach utilized in our practice.

	Permethrin or oral ivermectin	Skin biopsy (H&E and/or DIF)	Medication Switch
Number of Patients (%)	55/106 (51.9%)	54/106 (50.9%)	8/106 (7.5%)
Clinical Utility (%)	6/55 (10.9%) patients responded to empiric treatment for scabies	5/54 (9.3%) patients had a biopsy consistent with bullous pemphigoid	1/8 (12.5%) patient with resolution of pruritus after switching lisinopril to losartan

H&E: Hematoxylin and eosin; DIF: direct immunofluorescence

Table 3. Work-up approach in patients with and without prurigo nodularis

	Patients who received at minimum a CBC	Patients treated empirically for scabies	Patients who received a skin biopsy
Patients with Prurigo Nodularis (n=31)	25/31 (80.7%)	19/31 (61.3%)	18/31 (58.1%)
Patients with no skin lesions (n=75)	62/75 (81.3%)	37/75 (49.3%)	33/75 (44.0%)

CBC: complete blood count

Table 4. Approach to the patient with generalized idiopathic pruritus lacking primary skin lesions

Careful review of past medical history
Careful review of medications; consider switching ACEI to ARB
Careful physical examination including lymph nodes
CBC, CMP, Chest x-ray
Empiric permethrin
If patients fail anti-scabetic treatment and > age 65: Two skin biopsies (H&E and DIF)

ACEI: angiotensin-converting-enzyme inhibitor; ARB: angiotensin-receptor blocker; CBC: complete blood count; CMP: complete metabolic panel; H&E: hematoxylin and eosin; DIF: direct immunofluorescence

almost 11% of patients treated empirically for scabies had documented resolution of their pruritus. Of note, the duration of pruritus for these patients was typically in the order of weeks to months. Dermatologists must have a high index of suspicion for scabies in all elderly patients; even if living independently they may have exposure to family or friends in long-term care facilities. [14] Furthermore, the clinical presentation in elderly patients can be atypical and involve the face or spare the fingerwebs. [14] Treatment with topical permethrin alone has a high failure rate, likely secondary to physical limitations, and patients may need oral ivermectin. [14] In our cohort of six patients with confirmed scabies, two required oral ivermectin in

addition to topical permethrin, and a third patient required three treatments with topical permethrin.

Should patients fail empiric anti-scabetic treatment, we recommend skin biopsies in patients over the age of 60-65, as they are minimally invasive yet have marked implications for treatment and management. In our study, approximately 9% of the patients who received a biopsy had results that were consistent with bullous pemphigoid. The average age of these patients was 77.4 years and the duration of pruritus ranged from 3 months to 10 years. We would like to highlight three of the patients ultimately diagnosed with bullous pemphigoid. One patient carried a diagnosis of eczema. His laboratory work-up illustrated peripheral eosinophilia but normal serum levels of immunoglobulin E, yet he did not present with eczematous lesions. He had failed oral anti-histamines, oral gabapentin, and narrow-band ultraviolet B. A second patient had a diagnosis of essential thrombocythemia, which itself is associated with severe, generalized pruritus. [15] A third patient had a low level of serum thyroid-stimulating-hormone level. There is conflicting evidence regarding the association between generalized pruritus and thyroid disorders and empiric testing for thyroid disorders in the absence of symptoms is not recommended. [9] Of note, two patients in our study had false positive serology results for auto-antibodies to bullous pemphigoid as their biopsy results were negative, thus stressing the importance of obtaining tissue samples. Indeed, in a study of 337 patients without bullous pemphigoid, 25 (7.4%) tested positive for autoantibodies to bullous pemphigoid antigen II (BP180) and/or bullous pemphigoid antigen I (BP230), with negative results by indirect immunofluorescence. [16] With regards to discontinuation of medications, there are published reports about the association between calcium channel blockers and chronic eczematous dermatoses, [17] yet in our experience, we have had more success with the discontinuation of ACEI.

There are several weaknesses and limitations to our study. First and foremost, the information gleaned from a retrospective chart review is not always complete. For example, patients without documented laboratory or biopsy results may have had such tests performed at outside doctors. With regards to the patients who responded to anti-scabetic treatment, we were not able to document scabies objectively. In addition, it is possible that the same treatments could have unforeseen effects on demodex, which would also alleviate itch. Furthermore, there may have been a placebo response. With regards to the patients ultimately diagnosed with bullous pemphigoid, we acknowledge that bullous pemphigoid is a clinical diagnosis supported by laboratory findings.

In our practice, we have had patients who, following a positive DIF with no skin lesions, subsequently developed bullae. We acknowledge that others would not give them a diagnosis of bullous pemphigoid and would simply say they had a positive DIF. In addition, although the nature of our study precluded us from being able to do the following – it would be of interest to ask the patient what they consider to be the cause of their pruritus. Doing so may elicit helpful clues from the patient, but could also, in certain circumstances, point towards a diagnosis such as delusions of parasitosis.

Another weakness of this study is the lack of long-term follow-up, most relevant to finding out whether patients developed underlying

medical disorders such as bullous pemphigoid, atopic dermatitis, or other underlying medical reasons that could explain the development of generalized pruritus. This information would best be garnered from a prospective study.

CONCLUSION

Generalized pruritus is a common chief complaint and one that is often frustrating for patients and their providers. The guidelines published by the British Association of Dermatologists provide a clinical approach for patients who lack primary skin lesions. The results of our study suggest that empiric treatment for scabies with topical permethrin should be considered as well. In addition, skin biopsies to rule out subclinical bullous pemphigoid should be considered for all patients over the age of 60-65. Lastly, dermatologists may consider replacing an ACEI for an ARB. Our hope is that having more evidence-based guidelines to provide a step-by-step approach will help dermatologists and primary care physicians be well equipped to manage this common outpatient complaint.

Abbreviations:
ACEI: Angiotensin-converting-enzyme inhibitor
BAD: British Association of Dermatologists
CBC: complete blood count
Chest CT: chest computed-tomography
BP bullous pemphigoid
H&E: Hematoxylin and Eosin
DIF: Direct immunofluorescence
ARB: angiotensin-receptor-blocker
BP180: Bullous pemphigoid antigen II
BP230: bullous pemphigoid antigen I

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