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Thoracoabdominal computed tomography neoplasia detection in patients with paraneoplastic pemphigus: the importance of collaboration between specialists

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Abstract

Introduction: Paraneoplastic pemphigus (PNP) is an autoimmune disorder that is almost always linked to an underlying neoplasia. General radiologists are usually not aware of what kind of neoplasia can be associated with PNP. Therefore, this study evaluates the effect of a dermatology lecture on radiologists' neoplasia diagnosis performance.
Methods: Two radiologists evaluated thoracoabdominal computed tomography (CT) examination images of 43 patients with PNP in separate reading sessions blinded to each other's assessments. Six months after the first CT image evaluation session, the two radiologists attended a lecture by two dermatologists about PNP, and 6 months later the two radiologists assessed the same CT examinations again.
Results: Statistical analysis showed statistically significant differences in CT sensitivity between the first and the second round of image evaluation for both radiologists (reader 1: $p = 0.0313$; reader 2: $p = 0.0156$).
Conclusions: This is the first study to evaluate the effectiveness of a dermatology lecture on diagnostic performance. It is very important for radiologists to be familiar with the particular neoplasms that can be associated with PNP because this can have a direct clinical impact on diagnostic performance.

Keywords: paraneoplastic pemphigus, neoplasia, radiology, computed tomography, detection

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Introduction

Paraneoplastic pemphigus (PNP) is a rare autoimmune disorder with painful mucosal erosions and polymorphous cutaneous lesions that may be blistering, erosive, or lichenoid (1). The exact incidence of PNP is unknown; however, it is estimated in Europe at about one case per million (2). The earliest sign is ulcerative/erosive stomatitis, which is difficult to resolve and is often associated with serohematous crusts and erythema on the lips (3). Clinical manifestations vary and resemble other diseases, such as pemphigus, pemphigoid, erythema multiforme, graft-versus-host disease, and lichen planus (4). A unique feature of PNP is that direct immunofluorescence shows an intracellular pattern of IgG and C3, and linear or granular IgG deposition along the basement membrane (5).

PNP places a great burden on patients, with a mortality of about 90%, and it mostly affects the age group between 45 and 70 years (6). This disease is very frequently associated with various neoplasms and requires careful patient evaluation (1).

According to the Italian Guidelines on Pemphigus, a chest X-ray and abdominal sonography are optional for these patients, but the patient's general condition and neoplastic comorbidities should be assessed (7). In fact, neoplasia could be associated with pemphigus, particularly in the rare pemphigus variant called PNP, which accounts for about 5% of pemphigus cases (8). This variant is reported to be primarily associated with hematologic malignancies, but a minor share of neoplasms associated with PNP represents non-hematologic neoplasms, including neoplasms originating from the thymus (e.g., thymoma), sarcoma, malignant melanoma, and various epithelial-origin carcinomas (e.g., adenocarcinoma and squamous cell carcinoma) (3).

To our knowledge, only one case series of six patients with Castleman disease and a few case reports with computed tomography (CT) images have been published (9–12). Therefore, radiologists' awareness about PNP-associated neoplasia is low. Accordingly, this study evaluates the effect of a dermatology lecture on radiologists' diagnoses of neoplasia.

Methods

From January 1st, 2000 to December 31st, 2019, 49 patients with PNP were identified in a database (Dermatology Clinic, Polytechnic University of Marche, Italy). The inclusion criteria were PNP diagnosis based on histological examination, serological tests, direct immunofluorescence microscopy, and thoracoabdominal CT performed at our hospital within 1 month after clinical suspicion of PNP. Patients with a previous neoplasm diagnosis were excluded. Following these criteria, 43 patients (mean age 59 years; range 39–78; 23 males) were included in the study. The study was approved by the institutional review board and ethics committee of our institution. Informed consent was obtained from all participants included in the study.

According to Camisa et al., three major criteria, or two major and two minor criteria, are required to diagnose PNP (13, 14). Major criteria include polymorphic mucocutaneous eruptions, concomitant internal neoplasm, and serum antibodies with a specific

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immunoprecipitation pattern. Minor criteria include acantholysis observed histologically, direct immunofluorescence displaying intercellular and basement membrane staining, and indirect immunofluorescence staining positive on rat bladder epithelium.

All CT examinations were performed using a 64-slice CT scanner (Lightspeed VCT 64, GE, Milwaukee, WI, United States) with patients in a supine position and feet toward the gantry. The scan parameters were as follows: scan range from lung apices to pubis level, 64 × 0.625 mm beam collimation, 120 kVp, 2.5 mm slice thickness, and 2.5 mm slice thickness reconstructions. After a precontrast scan, 80 to 100 ml of non-ionic iodinated contrast material (iopamidol, 370 mg of I/ml; Bracco Imaging, Milan, Italy) was administered at a flow rate of 3.5 ml/s followed by 40 ml of saline solution at 3.5 ml/s via the antecubital vein. An abdominal dual-phase dynamic CT scan was performed at 20 to 35 sec (hepatic arterial phase) and 65 to 75 sec (portal venous phase) after injection.

Two radiologists evaluated the CT examination images: one was a radiologist with at least 10 years' experience in thoracoabdominal CT, and the other was a resident in his last year of radiology residency. Before CT image evaluation, the two radiologists were informed about the patients' skin pathology. However, they were blinded to the lesion final pathology on surgical excision reports. The two radiologists retrospectively assessed CT images in separate reading sessions blinded to each other's assessments. For blinding purposes, the PNP thoracoabdominal CT examinations were mixed into a stack of approximately 80 other thoracoabdominal CT examinations of patients with other skin pathologies, for a total of 120 examinations. For each examination, the radiologists were allowed a maximum evaluation time of 5 minutes, at the end of which they had to report suspicious CT findings (lesions, masses, lymphadenopathies, and splenomegaly).

Six months after the first CT image evaluation session, the two radiologists attended a lecture by two dermatologists about PNP, during which the incidence and target organs of the various associated neoplasm were listed.

Twelve months after the first CT image evaluation session, the two radiologists retrospectively assessed the same 120 CT examinations in separate reading sessions blinded to each other's assessments and blinded to the lesion final pathology on surgical excision reports. As for the first round, PNP thoracoabdominal CT examinations were mixed into the same stack of approximately 80 other thoracoabdominal CT examinations, and for each examination the radiologists were allowed a maximum evaluation time of 5 minutes, at the end of which they had to report CT findings.

Focal thoracic or splanchnic CT density modification not clearly attributable to non-neoplastic lesions (such as cystic lesions, lithiasis, or bowel diverticula) and moderate or severe splenomegaly were considered positive findings. A reading was qualified as true positive when a positive finding was associated with a neoplastic lesion at final pathology in the surgical excision report or bone marrow biopsy report. A reading was qualified as false negative when a positive CT finding was not identified and a neoplastic lesion was not reported at final pathology in the surgical excision report or bone marrow biopsy report. Qualitative variables were evaluated using McNemar's test. The statistical significance level was set at $p < 0.05$. All statistical analyses were performed using MedCalc Software v. 15.8 (Ostend, Belgium).

Results

A neoplasm was found in 43 patients, and all underwent surgery or bone marrow biopsy. Final pathology results after surgical excision are reported in Table 1.

In the first round of CT evaluation, 37 (86.1%) and 36 (83.7%) out of 43 suspicious findings were detected by the first and second reader, respectively. Multiple lymphadenopathies and/or splenomegaly were found in 16 patients. One patient showed a 6.5 cm lesion in the right hemipelvis. Four patients showed lung lesions. Conspicuous gastric antrum masses were found in two patients. In two patients a thymic mass measuring about 3 cm was detected. Three patients showed kidney masses. One patient showed inhomogeneous retroperitoneal adipose tissue in the left flank. Five patients showed colorectal wall thickening. Two patients showed pancreatic lesions. The radiologist with at least 10 years of experience also reported a gallbladder lesion (Fig. 1).

One year later, during the second round of CT evaluation, 43 (100%) suspicious findings were identified by both radiologists. All the lesions detected during the first round were also found in the second round. Moreover, a small thymic mass (Fig. 2), an anterior rectal wall thickening of about 1 cm (Fig. 3), one small gastric lesion (Fig. 4), and three moderate splenic enlargements were detected by both radiologists; the radiology resident also reported the gallbladder lesion (Table 2).

Table 1 | **Final pathology on surgical excision or diagnosis after bone marrow biopsy.**

Patients, *n*	Lesion histology
12	Non-Hodgkin lymphoma
7	Chronic lymphocytic leukemia
3	Gastrointestinal stromal tumor (two gastric, one colorectal)
3	Thymoma
4	Lung adenocarcinoma
1	Inflammatory myofibroblastic tumor
1	Liposarcoma
1	Gallbladder cancer
3	Clear cell renal cell carcinoma
5	Colorectal adenocarcinoma
2	Pancreatic tumor
1	Gastric adenocarcinoma

Table 2 | **Suspicious findings reported by the two readers in the first and second rounds.**

	First round		Second round	
Suspicious findings	**1st reader**	**2nd reader**	**1st reader**	**2nd reader**
Lymphadenopathies and/or splenomegaly	16/19	16/19	19/19	19/19
Colorectal wall thickening	5/6	5/6	6/6	6/6
Lung lesions	4/4	4/4	4/4	4/4
Kidney masses	3/3	3/3	3/3	3/3
Thymic masses	2/3	2/3	3/3	3/3
Gastric masses	2/3	2/3	3/3	3/3
Pancreatic lesions	2/2	2/2	2/2	2/2
Retroperitoneal adipose tissue lesion	1/1	1/1	1/1	1/1
Right hemipelvis mass	1/1	1/1	1/1	1/1
Gallbladder lesion	1/1	0/1	1/1	1/1
Sum of all suspicious findings	37/43	36/43	43/43	43/43

The McNemar test showed statistically significant differences of CT sensitivity between the first and second rounds of image evaluation (reader 1: $p = 0.0313$; reader 2: $p = 0.0156$).

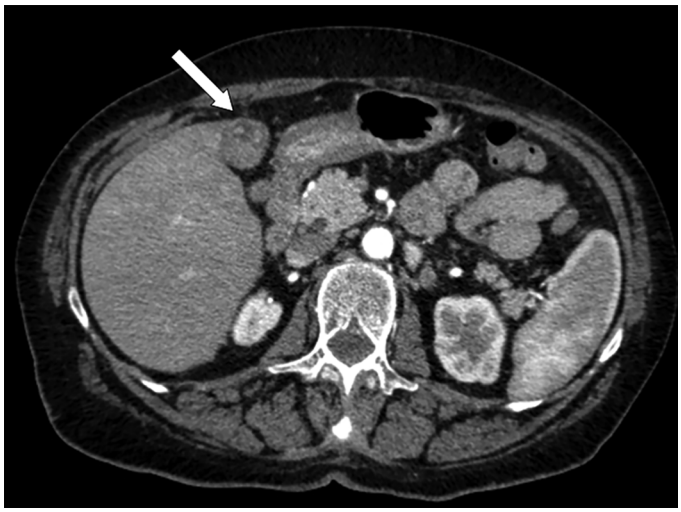

Figure 1 | Soft tissue mass lesion in the gallbladder fundus in a patient with gallbladder adenocarcinoma.

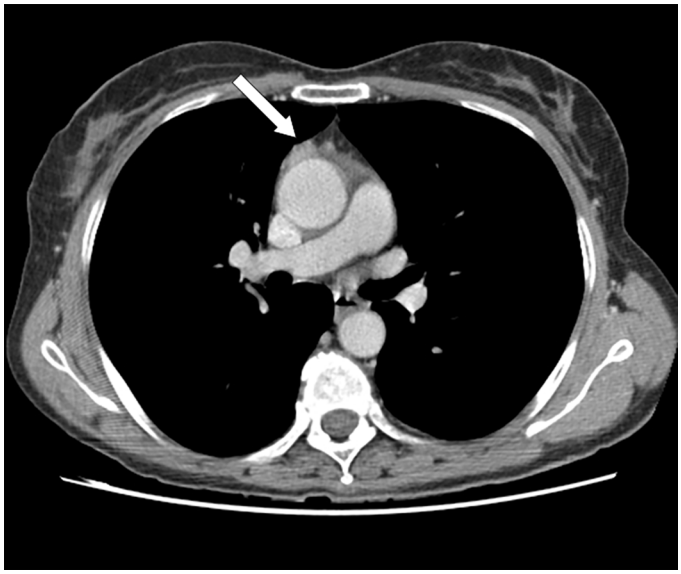

Figure 2 | A thymic mass measuring about 1 cm that proved to be a thymoma in final pathology after surgical excision.

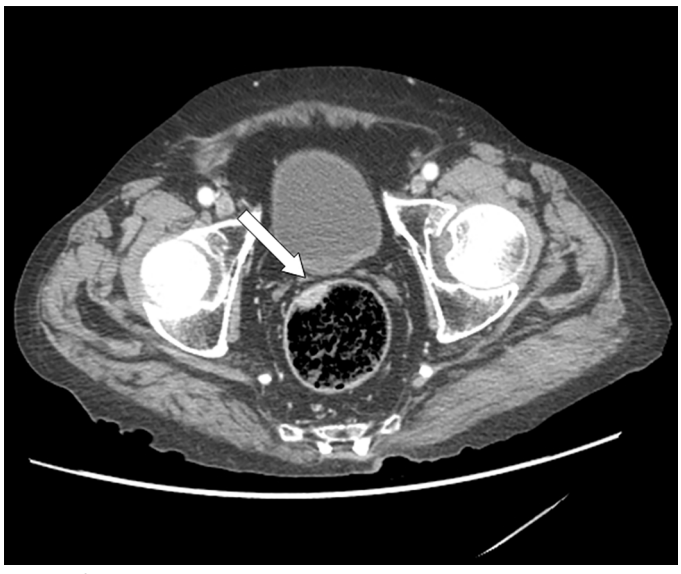

Figure 3 | A small rectal wall thickening that proved to be a gastrointestinal stromal tumor in final pathology after surgical excision.

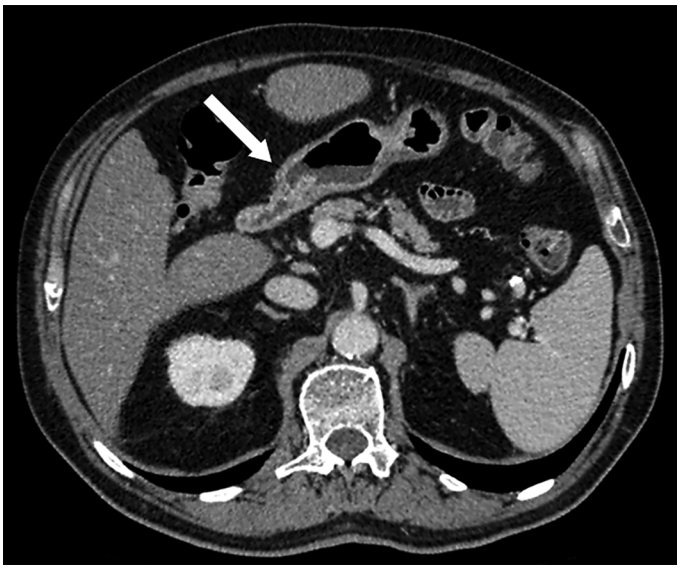

Figure 4 | A gastric mass that proved to be a low-grade adenocarcinoma in final pathology after surgical excision.

Discussion

PNP is a rare disease because it represents a small percentage of patients with autoimmune blistering diseases of the skin. The term *paraneoplastic autoimmune multiorgan syndrome* was coined to account for the variable non-bullous cutaneous manifestation and additional systemic findings, such as bronchiolitis obliterans (2, 15).

It is known that PNP is very frequently associated with neoplastic diseases, mostly a lymphoproliferative disorder. However, only a previous study examined the role of diagnostic imaging in these patients (16).

This study evaluated CT scans in PNP patients managed by a tertiary urban referral academic dermatologic clinic. All CT examinations showed a tumor or a suspicious finding, such as splenomegaly, and a neoplasm was finally diagnosed in all patients. This is in contrast with previous published studies, which reported that about 10% of patients did not show a neoplastic lesion at PNP diagnosis (4, 17). Perhaps this could be related to the fact that all patients in this study underwent a CT scan. In fact, Lehman et al. reported that diagnostic imaging is likely to detect underlying neoplasms in patients with unknown malignancy (16).

We reported a slightly lower percentage of hematologic disease with respect to previous published studies (4, 17, 18). In fact, in this study 19 out of 43 (44.2%) patients with associated PNP tumors showed a non-Hodgkin lymphoma or chronic lymphocytic leukemia. In contrast, previous studies reported that non-Hodgkin lymphomas and chronic lymphocytic leukemia were about 45% and 15% of the tumors associated with PNP, respectively (4, 18).

Moreover, in our study population no Castleman disease was found. This is in contrast with previous published studies, in which it represented about 15% of the neoplastic conditions associated with PNP (19, 20).

The differences in hematologic diseases in our PNP patients and those reported in the literature could be partially explained by the fact that the research was performed using a dermatologic database, and perhaps some patients with PNP were entirely managed by hematologists. Therefore, dermatologists did not meet these patients, probably not even during a dermatologic consultancy.

PNP could be associated with various cancers. However, in rare cases common cancers such as adenocarcinomas of breast, bowel, and lung have been associated with PNP (4). Moreover, it is also associated with specific neoplasms that are not so frequently encountered in clinical practice. These are inflammatory myofibroblastic tumors, gastrointestinal stromal tumors, retroperitoneal sarcomas, and thymomas (21–28).

Therefore, regarding the clinical implications of this study, it is very important for a radiologist to be familiar with those particular neoplasms that could be associated with PNP. This is not only important in practice, but it could also have a direct clinical impact on diagnostic performance. In fact, familiarity with this association means that radiologists could pay more attention to searching for some tumors that are not so simple to recognize in a rapid thoracoabdominal evaluation, as they are sometimes obliged to do during their routine clinical practice. For example, a gastrointestinal stromal tumor in the small intestine is not simple to recognize unless a careful evaluation of the gastric, duodenal, jejunum, ileum, and rectal walls is performed. The same difficulty can occur when a thymoma is suspected; in fact, a small prevascular mass cannot always be easily and quickly identified. Increased attention to endoluminal content evaluation along the entire gastrointestinal tract can also increase the detection of other endoluminal malignancies, such as adenocarcinomas. Moreover, splenomegaly can sometimes be the only sign of a non-Hodgkin lymphoma. Radiologists must bear in mind the need to measure the spleen, also by evaluating the spleen area, so that they do not fail to report a moderate splenomegaly that could be the only sign of cancer in PNP patients, particularly non-Hodgkin lymphoma such as splenic marginal zone lymphoma. Therefore, familiarity with possible tumor locations and CT signs in these patients can help radiologists recognize lesions more easily and faster because they know what to search for.

This study has some limitations. First of all, it is a single-institution analysis. However, this is a tertiary urban referral teaching hospital, in which dermatology has its own ward. Moreover, the patient cohort consisted of a relatively small number of patients, considering the rarity of this condition. However, to the best of our knowledge, this is the first study that targets radiologists to make them aware of tumors associated with PNP and that evaluates the effectiveness of a dermatologic lecture on diagnostic performance.

In conclusion, with regard to dermatological diseases and specifically PNP, the greater radiologists' knowledge of the pathologies they encounter in the course of their clinical practice, the greater their ability to provide adequate answers to the clinicians and the patients they work with. In the authors' opinion, this study could help foster collaboration between dermatologists and radiologists with the aim of achieving better disease diagnosis and management.

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