

# Mediastinal Lymph Node Metastasis of Lung Cancer with an Unknown Primary Lesion Having Concurrent Endocrine Abnormality and Acanthosis Nigricans: Report of a Case

Naoyuki Yoshino, MD,<sup>1</sup> Shigeki Yamagishi, MD,<sup>1</sup> Hirotoshi Kubokura, MD,<sup>1</sup>  
Iwao Mikami, MD,<sup>1</sup> Tomomi Hirata, MD,<sup>1</sup> Kiyoshi Koizumi, MD,<sup>1</sup> Tetsuya Okano, MD,<sup>2</sup>  
Ayako Futagami, MD,<sup>3</sup> Masashi Kawamoto, MD,<sup>4</sup> and Kazuo Shimizu, MD, FACS<sup>1</sup>

We herein describe a patient we encountered in whom mediastinal lymph node metastasis of lung cancer with an unknown primary lesion was complicated by both an endocrine abnormality and acanthosis nigricans. A 66-year-old male visited a local hospital and was diagnosed as having acanthosis nigricans. The patient was referred to our hospital for further examination. Computed tomography scans of the chest and the abdomen showed no adverse findings except for an enlargement of the mediastinal lymph node. No malignant lesions were detected in examinations of the upper gastrointestinal tract. Based on the above findings, the lesion was thus considered to possibly be mediastinal lymph node metastasis of an unknown primary tumor or malignant lymphoma. A thoracoscopic biopsy of the mediastinal lymph node was performed. The patient was diagnosed to have mediastinal lymph node metastasis of lung cancer with an unknown primary lesion and endocrine abnormality resulting from paraneoplastic syndrome. Palliative radiation therapy was initiated to prevent superior vena cava syndrome and esophageal passage failure or dysphagia. The cutaneous lesions markedly improved thereafter. The serum levels of adrenocorticotrophic hormone decreased. (*Ann Thorac Cardiovasc Surg* 2009; 15: 397–400)

**Key words:** acanthosis nigricans, lung cancer, mediastinal lymph node

## Introduction

Acanthosis nigricans is a disease characterized by hyperpigmented, verrucous, velvety skin lesions that are typically located in skin folds.<sup>1</sup> These lesions are generally classified into malignant and benign diseases.<sup>2</sup> Acanthosis nigricans

associated with lung carcinoma has rarely been reported. Initially, this disease was thought to be found only in association with adenocarcinomas located mainly in the gastrointestinal tract.<sup>3</sup> We herein describe a patient we encountered in whom mediastinal lymph node metastasis of lung cancer with an unknown primary lesion was complicated by both an endocrine abnormality and acanthosis nigricans.

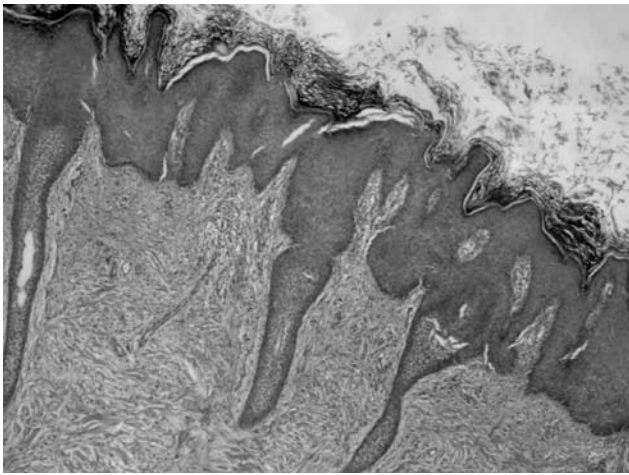
## Case Report

A 66-year-old male visited a local hospital with the chief complaints of general malaise, hyperpigmentation of the skin, and weight loss. The patient was diagnosed to have acanthosis nigricans (Fig. 1). Cushing's syndrome was

From <sup>1</sup>Division of Thoracic Surgery, Department of Surgery; <sup>2</sup>Department of Internal Medicine; <sup>3</sup>Department of Dermatology; and <sup>4</sup>Department of Pathology, Nippon Medical School, Tokyo, Japan

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Address reprint requests to Naoyuki Yoshino, MD: Department of Thoracic Surgery, Saitama Cancer Center, 818 Komuro, Ina-machi, Saitama 362-0806, Japan.

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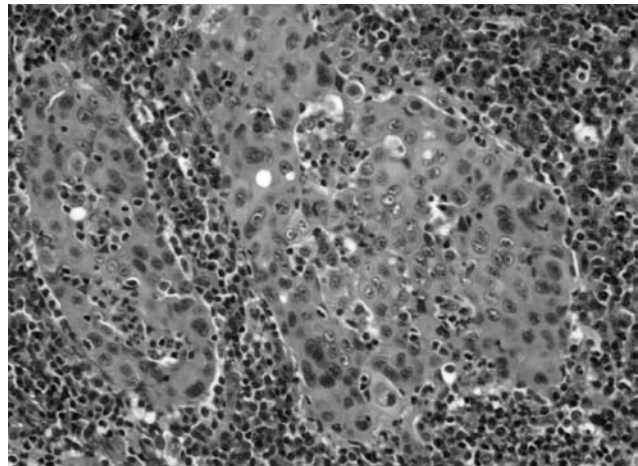


**Fig. 1.** A skin biopsy showed papillomatous hyperplasia of the epidermis, with hyperkeratosis and acanthosis.



**Fig. 2.** A chest CT scan revealed a marked enlargement of the mediastinal lymph node.

also suspected because elevations in adrenocorticotrophic hormone (ACTH) and cortisol levels were noted. The patient was referred to our hospital for further examination and was hospitalized in October 2006. Examinations were carried out because malignant neoplasms and endocrine diseases have commonly been reported as underlying disorders of acanthosis nigricans. Of the tumor markers assessed, carcinoembryonic antigen (CEA), squamous cell carcinoma antigen (SCC-Ag), and carbohydrate antigen 19-9 (CA19-9) were found to have increased. The endocrine function test using dexamethasone showed a normal cortisol suppression at dexamethasone levels of 0.5 mg and 1.0 mg, indicating that the possibility of Cushing's syndrome was ruled out. Diagnostic imaging revealed no pituitary lesions. Computed tomography (CT) scans of the chest (Fig. 2) and the abdomen showed no adverse findings except for an enlargement of the mediastinal lymph node. No malignant lesions were detected in examinations of the upper gastrointestinal tract. An 18-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) scan also showed no changes at any sites except the mediastinal lymph node. Based on these findings, the lesion was thus considered to possibly be mediastinal lymph node metastasis of an unknown primary tumor or malignant lymphoma. A thoracoscopic biopsy of the mediastinal lymph node was performed in the following month, November. Histopathologically, atypical cells presented with the nucleus containing a large acidophilic nucleolus and fine nucleoreticulum, together with palely stained cytoplasm, and some of them had adenoid structures. However, a definite diagnosis of adenocarcinoma was not made based on



**Fig. 3.** Atypical cells presented with the nucleus containing a large acidophilic nucleolus and fine nucleoreticulum, together with a lightly stained cytoplasm. Some had adenoid structures.

only the findings from hematoxylin and eosin staining (Fig. 3). Immunohistochemical staining showed the biopsy specimen to be positive for cytokeratin (CK) 7, negative for CK20, positive for thyroid transcription factor 1 (TTF-1), positive for villin, and negative for ACTH. Although a possibility of gastrointestinal tract involvement could not be categorically ruled out because the tissue was positive for villin and TTF-1, the CK pattern was not inconsistent with pulmonary carcinoma.

Based on these results, the patient was diagnosed to have mediastinal lymph node metastasis of lung cancer with an unknown primary lesion and endocrine abnormality



**Fig. 4.** Skin findings.

**A:** Before radiation therapy.

**B:** After therapy. During the course of radiotherapy, the hyperpigmented epidermis began scaling off to gradually reveal the newly formed normal skin.

A | B

resulting from paraneoplastic syndrome. Palliative radiation therapy was initiated to prevent superior vena cava syndrome and esophageal passage failure or dysphagia. A CT scan of the chest performed after a radiation dose of 15 Gy to evaluate the response revealed the swollen lymph node to have decreased in size; therefore additional irradiation was carried out. The patient was discharged upon the completion of radiation therapy with a total dose of 57.2 Gy. The cutaneous lesions markedly improved thereafter (Fig. 4). The serum levels of ACTH decreased from a peak of 115.3 pg/mL to 39.1 pg/mL, cortisol from a peak of 19.5  $\mu$ g/mL to 10.1  $\mu$ g/mL, and the CEA from a peak of 7.1 ng/mL to 3.2 ng/mL.

## Discussion

Acanthosis nigricans is a disease characterized by hyperpigmented, verrucous, velvety skin lesions that are typically located in skin folds.<sup>1)</sup> Patients with this disease are mainly divided into two categories: those who develop acanthosis nigricans as a part of paraneoplastic syndrome, and those who have systemic disorders characterized by tissue resistance to insulin, presenting more diverse clinical features than the former patients. The etiology of acanthosis

nigricans has not been clarified.<sup>3)</sup> Several investigators have suggested that a tumor-produced humoral factor could possibly play a role in the development of this disease. Various peptides such as urogastrone, ACTH, human growth hormone, and thyroid-stimulating hormone have also been implicated as being potentially causative factors. In 1997, Koyama et al. showed the coexpression of transforming growth factor (TGF)- $\alpha$  and epidermal growth factor (EGF) receptor to be detected in the gastric tumor cells of a patient with malignant acanthosis nigricans. EGF receptors can also be present in cutaneous lesions, whereas the level of TGF- $\alpha$ , which is higher in the serum, was noted to abruptly decrease after a total gastrectomy.<sup>2)</sup> Acanthosis nigricans associated with lung carcinoma has rarely been reported. Initially, this disease was thought to be found only in association with adenocarcinomas located mainly in the gastrointestinal tract, but it is now known to be associated with SCCs, lymphomas, and sarcomas.<sup>3)</sup> The results from two studies investigating 247 and 277 patients with acanthosis nigricans, respectively, revealed that intra-abdominal malignancies were still commonly associated with this disease, being found in 185 (74.9%) and 203 (73.2%) patients of the 247 and 277 patients, respectively. Lung carcinomas were also found in 21 (8.4%) and 13 (4.7%) of these patients.

In the present case, although a diagnosis of pulmonary carcinoma was made, the primary tumor lesion remains unclear. Gross et al. reported that metastases of an unknown primary tumor were noted in 11 of 247 patients with malignant acanthosis nigricans.<sup>4)</sup> Patients having lung carcinoma with an unknown primary tumor should therefore be closely monitored by the performance of FDG-PET and other examinations because the primary neoplastic lesion may be detected later. In this case, lung cancer and endocrine abnormality concurrently presented. Based on the findings at presentation and the findings of reports indicating hyperpigmentation to be noted even in patients with Cushing's syndrome, we thought that these factors might thus be responsible for the development of acanthosis nigricans. However, the possibility of ectopic ACTH syndrome was ruled out because cortisol suppression was shown in the dexamethasone test, and histopathology revealed negative results for ACTH. The increased ACTH level seen in this patient is thus considered to be ascribable to paraneoplastic syndrome associated with the advanced malignancy. The findings are thus considered to be noteworthy, in consideration of a suggestion by Rigel et al. that ACTH can also be responsible for the development of acanthosis nigricans.<sup>5)</sup> It is most likely that some of the reported cases might therefore have also demonstrated conditions similar to those observed in the present case.

Kaneshige et al. showed the prognosis to be poor in most patients with acanthosis nigricans when they were aware of skin eruption, because by that time the underlying malignancy has already become advanced; therefore only a few such patients would have been followed up for changes in skin eruptions associated with acanthosis nigricans after having been treated for the tumor.<sup>6)</sup> Clarke described a patient whose skin condition improved after two short

courses of radiotherapy, but worsened again as metastases developed. On the other hand, Moller et al. showed that skin lesions in a patient with acanthosis nigricans completely resolved after a surgical resection of the tumor.<sup>3)</sup>

In the present case, the cutaneous manifestations began improving during the course of radiation therapy and then virtually subsided early following the therapy. Postoperative CT scans after 4 months of treatment revealed no mediastinal lymph node enlargement, thus indicating that the cutaneous manifestations progressed in parallel with the changes in size of the tumor. The patient will continue to be closely followed by appropriate diagnostic examinations.

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