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MALIGNANT ACANTHOSIS NIGRICANS—A PARA-ENDOCRINE SYNDROME?

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Abstract. A case is reported of acanthosis nigricans associated with a gastric carcinoma. The gastric cancer was of the diffuse, infiltrating type. Many tumour cells were identified by means of histochemistry and electron microscopy as neoplastic enterochromaffin-like cells. It is suggested that cancers associated with acanthosis nigricans might constitute a certain group of carcinomas in which parts of the tumour cells arise from the APUD-series of endocrine cells.

Key words: Acanthosis nigricans; Para-endocrine syndrome; APUD-cells

Acanthosis nigricans (a. n.) is a hyperpigmented, verrucose and hyperkeratotic dermatosis primarily affecting the flexural areas of the body. It occurs in two types (2) the malignant type associated with a cancer of an internal organ, and the benign type, not so associated. The associated tumour in malignant a. n. is usually an adenocarcinoma which, in around 90% of the cases, is reported to be intra-abdominal, most commonly located to the stomach (3, 5).

In this study a gastric carcinoma from a patient with a. n. was examined by light- and electron microscopy in order to determine if the tumour possessed certain characteristics different from other carcinomas.

CASE HISTORY

The patient, a 71-year-old woman, was admitted to the Department of Dermatology where a. n. was diagnosed and a search for a malignant tumour was undertaken.

The skin in the flexural areas of the body was hyperkeratotic and verrucose, having a dirty brownish colour (Fig. 1). Furthermore, several papillary verrucose lesions were seen on the hands (Fig. 2), arms, trunk and abdomen. Around the mouth and on the eyelids, more or less prominent condylomata acuminata-like lesions were seen. Later, the skin of both palms and on the nipples became dry and hyperkeratotic.

The various elements were very much like common warts and had no similarity with seborrhoeic keratoses as described in the Leser Trélat sign (6).

Investigations

The BSR was 43 mm/hr, but apart from this, the blood picture was normal. At oesophagoscopy, some verrucose lesions were observed in the lower part of oesophagus. Barium meal revealed a reduced gastric peristalsis.

Although no complaint of dyspepsia had been made and no definite signs of malignancy had been found, an exploratory laparotomy was performed based solely on the impaired gastric peristalsis and because of the knowledge that a. n., at the age of the present patient, is so frequently associated with a gastric neoplasm.

At operation, a gastric cancer of the diffuse infiltrating type was found, involving the whole stomach wall, spreading to the gastrocolic omenta and to perigastric lymph nodes. A total gastrectomia and oesophago-jejunostomia *a. m.* Roux was performed. At microscopy, tumour was found in the proximal resection line, proving that the operation was not radical.

One week postoperatively the cutaneous lesion showed regression. Thus the skin became lighter and softer and no further warty growths developed. A few weeks later the patient died.

Post-mortem examination

At autopsy, metastases to the liver and pre-aortic lymph nodes were found. No tumour was observed in the lines of resection. The verrucose lesions in the lower oesophagus, observed at oesophagoscopy some weeks before operation, were no longer present.

MATERIAL AND METHODS

Biopsies were taken from the skin, from various parts of the gastric carcinoma and from the perigastric lymph nodes. All specimens except the lymph node biopsies were prepared for light- and electron microscopy. The methods applied are specified in Table I.

Because of the close resemblance of the skin tumours to vulgar warts, specimens from the skin and peroperative

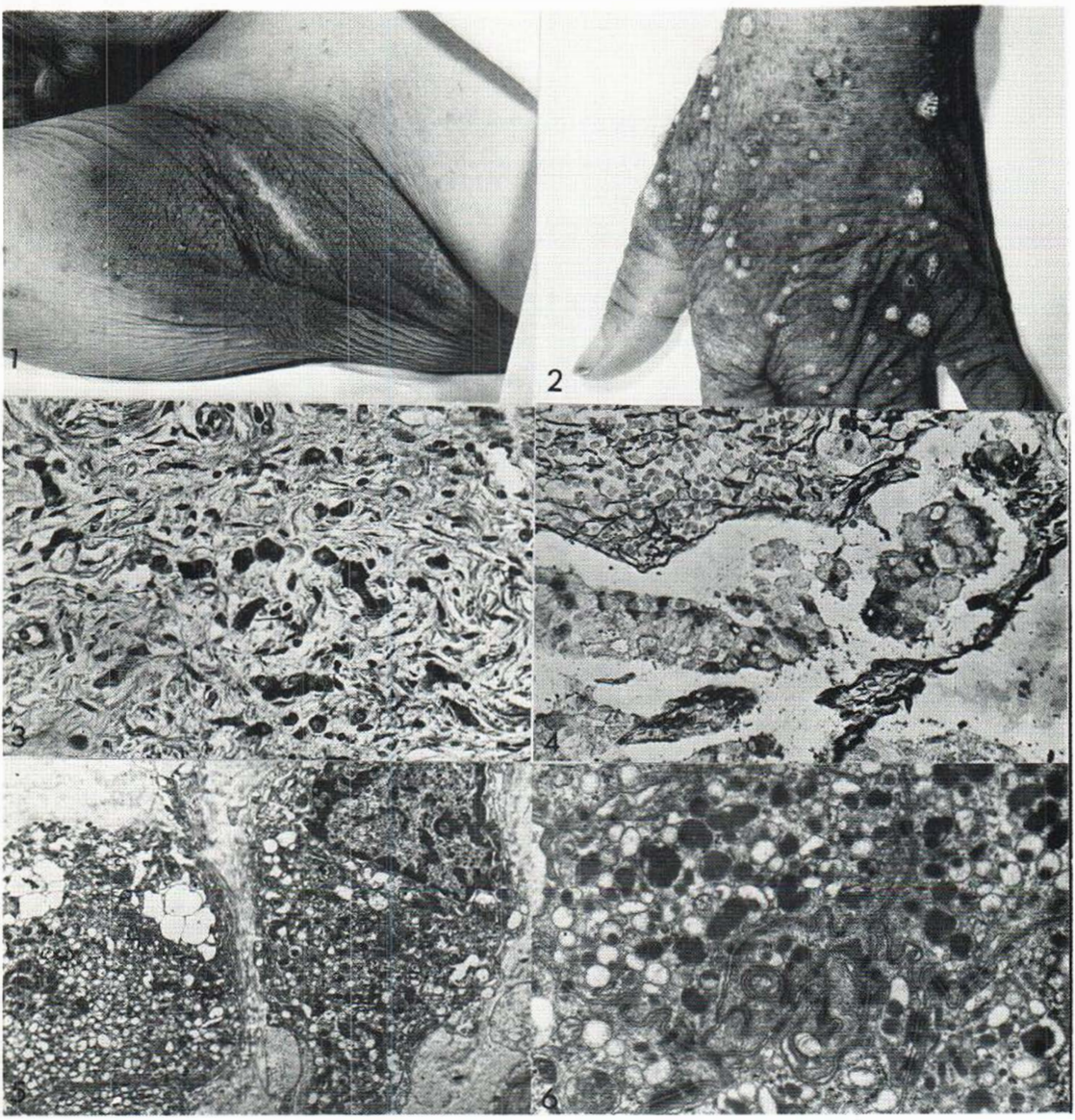

Fig. 1. The diffuse discoloured, warty surface of the right axillae of a patient with acanthosis nigricans.

Fig. 2. Papillary, verrucose lesions on the left hand of a patient with acanthosis nigricans.

Figs. 3, 4. Light micrographs of a gastric carcinoma (3) and of a lymph node metastases (4) from a patient with acanthosis nigricans, showing ECl-cells stained by the argyrophil silver methods of Grimelius (3) and Sevier-Munger (4)× 100.

Figs. 5, 6. Electron micrographs of a gastric carcinoma from a patient with acanthosis nigricans, showing ECl-cells with characteristic cytoplasmic secretory granules (5) ×4.200, (6) ×11.000.

biopsy specimens of the gastric carcinoma were prepared for papilloma virus identification, according to the technique described by Genner (7). At the same time, with an interval of about 6 weeks, samples of serum were examined for complement fixing antibodies against papilloma virus (8).

RESULTS

The microscopic picture of the dermatosis was that of a. n. The structure of the gastric cancer was varied. Tumour cells were arranged in cords or masses surrounded by thin bridges of vascular

Table I. *Methods applied to specimens from a gastric ECl-oma*

Methods	Results
Argyrophil	
Grimelius (9)	+
Sevier-Munger (14)	+
Argentaffin silver reaction Vialli (17)	÷
Lead-haematoxylin Solcia et al. (16)	÷
HCl-toluidine blue Solcia et al. (15)	÷

stroma, occasionally forming rudimentary glands, or individual cells or groups of cells were surrounded by abundant scar-like stroma.

By the various histochemical methods applied, many tumour cells from the stomach wall and the lymph node metastases were reactive to Grimelius' and Sevier & Munger's argyrophil silver methods (Figs. 3, 4). The cells failed to react with HCl-toluidine blue, lead haematoxylin, and Masson-Hamperl's argentaffin silver reaction.

At electron microscopy, many tumour cells were characterized by cytoplasmic secretory granules. These cells were of varying shape and size, often with long cytoplasmic processes. A closely interdigitating line was formed between the cells, often with well developed desmosomal connections. The most striking feature of the cells was the numerous secretory granules which almost filled the cytoplasm (Fig. 5). Membranes of adjacent secretory granules were in close contact or even fused with one another. Mostly the granules were made up of small, round or irregular dense cores eccentrically dispersed in large vesicles. Other granules were filled with rather dense or coarsely granular material surrounded by a thin halo or by closely applied membranes (Fig. 6).

Human papilloma (wart) virus was not found in specimens of skin lesions or tumour, and complement-fixing antibodies could not be demonstrated.

DISCUSSION

The dermatosis a. n. was classified in both benign and malignant forms by Curth (2). Many theories have been propounded with respect to the etiology of the disease and although Curth (3) described the macroscopic and microscopic identities of the two types, which suggested an identical origin, she later (4) stated that the two types showed enough differences to separate them.

The benign type of a. n. may be present at birth or begin in childhood but it appears most often around puberty. If symptoms start before puberty the cutaneous lesion tends to spread during puberty, suggesting a hormonal factor to be responsible. When this period is over the dermatosis either regresses or remains stationary. Genetic studies (4) have shown that benign a. n. is inherited as an irregular autosomal dominant trait, whereas a genetic basis of the malignant type of a. n. not was demonstrated.

In the malignant a. n. the average age at onset is 40 years (1) and it always seems to be associated with internal malignancy. Although the cancer may develop in a variety of organs, about 70% are gastric (3). Cutaneous involvement can precede, coincide or follow the clinical manifestation of the tumour. After treatment of the cancer the cutaneous lesion may subside or even disappear. However, spreading is invariably noted in cases of recurrence or metastasizing. The parallel course of a. n. and cancer suggests an intimate relationship possibly caused by some kind of humoral activator produced by the tumour and acting on the skin.

In the present case the macroscopic and microscopic pictures of the dermatosis were of a. n. By histochemistry and electron microscopy of the gastric carcinoma many tumour cells were identified as enterochromaffin-like (ECl) cells of the APUD-series of endocrine cells (12) and the tumour may thereby be classified as an APUDoma (13). Besides characteristic cytochemical and ultrastructural features (11), many of these cells are able to secrete polypeptide- or amine hormones.

In the human gastric mucosa the ECl-cells are the predominant endocrine cell type in the gastric fundus to which they are restricted (12). The normal ECl-cell has not yet been associated to any known hormone and an ECl-oma has never been described.

Montgomery & Welbourn (10) mentioned malignant a.n. as a possible para-endocrine syndrome in which the dermatosis arises through a humoral mechanism.

We suggest that in this case, functionally transformed tumour ECl-cells could produce a substance activating the dermatosis. Furthermore this could be a property shared by all the cells in the APUD-series of endocrine cells when becoming tumour

cells, thus giving an explanation for the various localizations of the malignant tumour in a. n. This also could explain why the dermatosis may subside after treatment of the cancer (as in this case) or even disappear, but invariably reappears upon renewed signs of cancer activity. Finally, because functioning neoplastic endocrine cells may only be a minor part of an otherwise non-endocrine tumour, they can easily be overlooked. This may explain why cancers in malignant a. n. have not yet been recognized as a distinct biological group.

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