The Acanthosis Nigricans Associated with Gastric Adenocarcinoma and Neurofibromatosis

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✔ We presented a case of acanthosis nigricans who exhibited an internal malignancy and neurofibromatosis.
The patient who is 45 years old had pruritus and axillary and inguinal discoloration resembling Acanthosis nigricans. The diagnosis was confirmed by the biopsy of the skin. The tomographic, endoscopic, and histopathologic singular revealed a poorly differentiated gastric carcinoma of the corpus which was at advanced stage. There were macules in close similarity with café au lait macules, and skin-colored, pedinculated soft nodules. The histopathologic diagnosis of neurofibroma was confirmed by the excision of one of the nodules.
Key words: *Acanthosis nigricans, gastric adenocarcinoma, neurofibromatosis*

✔ **Akantozis Nigrikans ile Birlikte Gastrik Adenokarsinom ve Nörofibromatozis**
İnternal malignite ve nörofibromatozis ile birlikte akantozis nigrikans olgusunu sunuyoruz.
Kaşıntı ve akantozis nigrikansı çağrıştıran aksiller ve inguinal diskolorasyon yakınmaları ile başvuran 45 yaşındaki erkek hastada tanı deri biyopsisi ile doğrulandı. Tomografik, endoskopik ve histopatolojik araştırmalarda mide korpusunda ileri evrede, az diferansiye adenokarsinom saptandı.Gövdede "cafe au lait" lekeleri ve deri renginde, pedinküle yumuşak nodüller mevcuttu. Histopatolojik olarak nörofibrom tanısı nodüllerin birinin eksizyonu ile doğrulandı.
Key words: *Akantozis nigrikans, gastrik adenokarsinom, nörofibromatozis*

INTRODUCTION

Acanthosis Nigricans (AN) is a distinctive dermatosis; consisting of hyperpigmented, velvety plaques with a predilection for the neck and flexural areas[1-3]. Neurofibromatosis is inherited as an autosomal dominant disorder and characterized by skin, bone and central nervous system lesions[2,3].

In this paper; a patient with Acanthosis Nigricans who also had internal malignancy and neurofibromatosis was presented in review with the recent literature.

CASE REPORT

A 45 years old man, with pruritus for 5-6 months, discoloration in axillary and inguinal areas (2-3 months), weight loss (15-20 days), nausea and vomiting was admitted our department.

Physical examination showed that he had mild cachexia and supraclavicular lymphadenopathy. Dermatological examination revealed extensive hyperpigmented, thickened and velvety plaques in flexural distribution which were most prominent on the

posterior and lateral aspects of his neck, and axillary, periumbilical, suprapubic, inguinal, antecubital and popliteal areas, and the dorsal surfaces of the hand (Figure 1). At palpation; lesions gave a feeling of thick, velvety, papillomatous plaques. Bilateral nipples and areolas had hyperkeratosis and hyperpigmentation (Figure 2).

AN was defined microscopically at the biopsy specimen (protocol number: 3695/97) from the skin of the posterior neck (Figure 3).

On the other hand, there were also hyperpigmented macular lesions that vary in size from 1 to 2 mm to 2 cm range, and in color from light to dark brown (café au lait) (Figure 1 and 2). There were skin-colored and pedunculated nodules that were very soft at palpation. Neurofibroma was defined histologically (protocol number: 4401/97) at the nodules.

Some tumor markers were elevated (AFP: 2.7mgr/dl, normal value: 0-7, β_2-microglobulin: 1892 mgr/dl normal value: 1010-1730 and CEA: 20.7 mgr/dl normal value: 0-5.2). All other laboratory tests were normal. Ultrasonographic examination of the abdominopelvic region showed thickened gastric wall and multiple enlarged lymph nodes at paraaortic and peripancreatic areas. Endoscopic examination of the upper gastrointestinal tract revealed edematous and hyperemic mucosa at gastric antrum and corpus of the stomach. The large polypoid neoplastic lumps occupied the entire lumen. The histological examination of the gastric biopsy specimens (protocol number: 4276/97) revealed poorly differentiated adenocarcinoma. Metastatic carcinoma was diagnosed at the biopsied supraclavicular lymph node (protocol number: 4257/97). Computerized tomography of the cervical region, thorax and abdomen showed multiple enlarged perigastric and paraaortic lymph nodes and gastric wall thickening.

Figure 1. Acanthosis nigricans with pigmented, velvety, papillomatous and cafe au lait spots and neurofibromas in back and neck and shoulder.

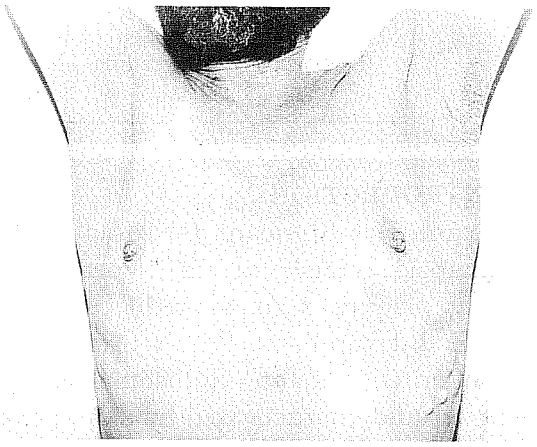

Figure 2. Acanthosis nigricans with pigmented, velvety, papillomatous lesions in bilateral axillae and neck.

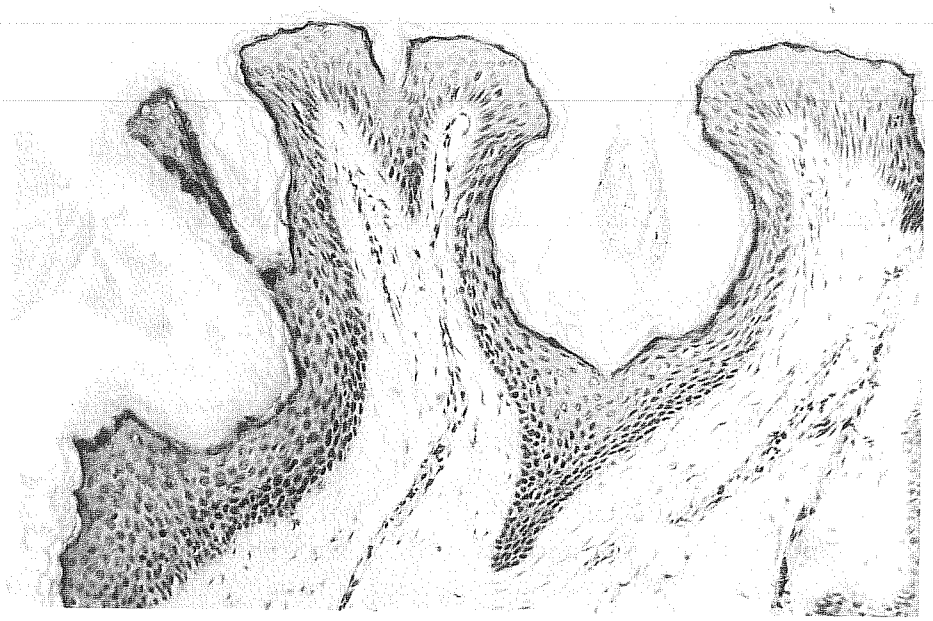

Figure 3. Acanthosis Nigricans. Hyperkeratosis, papillomatosis, irreguler acanthosis (x 200, H&E).

Depending on the clinical, laboratory and histopathological findings we diagnosed Acanthosis Nigricans in association with neurofibromatosis and gastric adenocarcinoma. Surgical therapy was not planned for gastric adenocarcinoma. The patient received a complete chemotherapy for his cancer.

DISCUSSION

AN was first described in 1890 by Pollitzer and Janovsky in independent reports[1-3]. Darier was determined AN associated with internal malignancy[4-6]. AN associated with malignancy usually appears in persons over 40 years of age. AN occurs in both sexes equally and has no apparent racial or geographical predilection[1-3]. Our case was a 45 year-old man with poorly differentiated gastric adenocarcinoma that had metastasis to the supraclavicular lymph node.

AN is probably caused by an elevated level of a factor stimulating keratinocytes and dermal fibroblasts at the cell receptor level. Theories regarding the cause of AN focus on the production of epidermal growth factor-like substances that may evoke the cutaneous changes[1,2].

Androgenic steroids, urogastrone (a potent gastric inhibitor similar in structure to human epidermal growth factor), ACTH, alpha-melanocyte stimulating hormone-like protein, human GH, TSH and APUD cell secretions have been proposed as causative factors of AN[1,3,6,7].

Neoplastic cells can release these peptides and peptide-like tumor secrete growth factor substances. The intensity of the lesions tend to show parallelism with the treatment of the tumor. Better results in the treatment of the associated malignancy often leads to regression of the skin and mucosal lesions. Recurrence of the tumor is followed shortly after by reappearance of the cutaneous and mucosal lesions[1,3].

AN may also result from extrinsic factors (e.g. nicotinic acid, glucocorticoids and

diethylstilbestrol) acting at the cell receptor level[1,2].

AN is a distinctive dermatosis consisting of hyperpigmented, velvety plaques with predilection for flexural areas, neck, inguinal and periumbilical regions. Sometimes there are verrucous and itchy plaques. Further it may involve other regions including the palms and soles, palpebra and mucous membranes. Papillation may be more evident than hyperpigmentation on the mucous membranes. Papillomatosis of the laryngeal, pharyngeal, esophageal and anogenital mucosa may sometimes be involved. Our case presented same cutaneous findings excluding mucous membrane involvement. In extreme cases, nearly the entire skin surface may be involved . The back of the neck was consistently the most severely affected site in children and was always involved when other areas were affected. In non-diabetic obese, hirsute hyperandrogenic women, the vulva was the most likely-site of involvement[1-3].

The first cutaneous change is hyperpigmentation, followed by intensified skin markings and varying degrees of hypertrophy of the epidermis without induration[2]. Early lesions may be difficult to detect clinically; histological verification may be useful[2]. Histologically the lesion reveals hyperkeratosis and papillomatosis, but only slightly irregular acanthosis and usually no hyperpigmentation[7]. In a typical lesion, the dermal papillae project upward as finger-like projections. The valleys between the papillae show mild to moderate acanthosis, and were filled with keratotic material. The epidermis at the tips of the papillae and often also on the sides of the protruding papillae appears thinned. The brown color of lesions is caused mostly from hyperkeratosis rather than melanin[7]. The histopathological examination of the skin biopsy specimen obtained from cervical region showed hyperkeratosis, papillomatosis, mild acanthosis, finger-like projections in dermal papillae. There was homogenization and predominantly perivascular lymphocytic infiltration in dermis.

Especially in malignant AN, the eruption may become almost generalized, soft papillomas and warty nodules may stud the affected surface. Papillomatous scalp involvement or progressive hair loss on the scalp, eyebrows, axillae, and limbs has been noted rarely[1-3]. This case was presented with the 2-3 mm diameter-papillomas on the affected skin surface, hair loss on the axillae and extremities. The nails may be striated and brittle (sometimes with longitudinal grooves or a patchy leukonychia) and may be thickened and completely whitened[1]. Especially in malignant acanthosis nigricans (MAN), hyperkeratosis of the nipples and areola, palms and soles have also been noted[1,2]. Our case displayed these findings. The oral cavity is affected in 25-50% of cases with MAN. Multiple soft small papillomas in the esophagus have been visualized on endoscopic and radiographic examination[2]. At endoscopy of this case, the esophagus had diffusely-located candidial plaques without any papillomatosis.

Acanthosis nigricans has always been classified into either benign or malignant form. Benign AN may be familial, drug induced or related to a variety of endocrinologic disorders and syndromes. Malignant AN is one of the cutaneous paraneoplastic syndromes[1-3]. Benign and malignant acanthosis nigricans are histologically identical. The malignant form differs clinically from the benign form by having a more rapid development and more extensive involvement. Many patients die within a year after the onset of the AN[1-3].

The most commonly reported tumor

associated with AN is adenocarcinoma, most often of gastric origin, followed by other intraabdominal sites[2]. In addition, MAN has been associated with gallbladder, bile ducts, prostate, pancreas, endometrium, over, thyroid, larynx, esophagus, colorectal carcinomas and rarely lung epidermoid carcinoma, mycosis fungoides, Hodgkin's and non-Hodgkin's lymphomas[1,2,4,5]. MAN associated frequently with Leser-Trélat Syndrome, Florid Cutaneus Papillomatosis, Muir-Torre[2,5,8,9].

The principal management should be directed at the underlying problem. However, topical keratolytics or podophyllin can be employed. Oral or topical retinoids, dermabrasion may also be used in these patients[1,2,10].

Neurofibromatosis (NF) is inherited as an autosomal dominant disorder. This case was presented with cafe au lait macules and neurofibromas. Microscopically, neurofibromas are formed by a combined proliferation of all the elements of a peripheral nerve; axons, Schwann's cells, fibroblasts. Schwann's cells frequently predominate, and usually have marked elongated nuclei, with a serpentine configuration and pointed ends[11]. In this case, the histopathological examination of nodules showed spindle cells, covered by squamous epithelium.

This our patient with terminal unresectable gastric cancer was lost after his follow-up at six months. Our case has been diagnosed as NF and AN associated with the development of gastric adenocarcinoma. Since, NF and AN both carry the increased risk of developing internal malignancy, occurrence of gastric adenocarcinoma in this patient is not surprising. But we could not find any report, carrying the features of this case for that reason. We think that occurrence of this disease is interesting.

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