

# Acanthosis nigricans and the sign of Leser-Trelat associated with primary brain tumor: Case report

Slobodan Stojanović<sup>1</sup>, Pavle Jeremić<sup>2</sup>, Mirjana Poljački<sup>1</sup>

## SUMMARY

The authors present a case of a female patient a 26-year old pensioner from Zmajevu, who developed skin changes in the neck region, armpits and groins, as well as in submammary folds during the 10 years period. The changes include dark-brown hyperpigmentation associated with sudden eruption of a large number of benign skin tumors and dark-brown seborrheic keratosis on trunk and extremities. In 1998, after magnetic resonance imaging, primary brain tumor of astrocytoma type with low grade of malignancy was discovered in thalamus region. The patient developed the above-mentioned skin changes since then. According to neurosurgical findings, the brain tumor is inoperable, so skin changes are persistent and stationary. Clinical changes correspond to paraneoplastic form of acanthosis nigricans. Numerous skin tumors histopathologically match seborrheic keratosis and reveal the clinical features of the sign of Leser-Trelat. It is interesting that in the same patient there are both, obligatory and optional, paraneoplastic dermatoses associated with malignant brain tumor.

**Key words:** Acanthosis Nigricans; Brain Neoplasms; Paraneoplastic Syndromes; Keratosis, Seborrheic

## INTRODUCTION

There are three clinical forms of acanthosis nigricans (AN) and their clinical and histopathological differentiation is difficult. These are malignant (paraneoplastic) form, hereditary autosomal dominant form (appears in childhood), and a form associated with endocrine disorders (pseudoacanthosis nigricans). Paraneoplastic form of AN is associated with carcinoma of internal organs (1, 2 and 3). These three forms of AN do not show significant differences histologically and clinically, so it should prompt an investigation for a hidden internal malignancy (1).

The sign of Leser-Trelat (SLT) is the sudden eruption of multiple seborrheic keratoses on skin of trunk and extremities. The association of this syndrome with internal malignancy has been described (1-5). It is considered a paraneoplastic dermatosis (1).

## CASE REPORT

**Present state of illness.** A 26-year old woman from Zmajevu came for a dermatological checkup in the Specialist Polyclinic of Clinical Center of Vojvodina at the beginning of 2007. She complained of pruritus (itching) and dark-brown calluses in the neck region, armpits and groins, as well as in submammary folds, accompanied by abrupt appearance of multiple "gray brown nodules", size of a grain of rice, on shoulders, back, belly, and extremities. The patient said that these changes had started to develop 10 years ago, but she had not paid attention to them or received any therapy, and the itching had not been significant. According to the patient's history of diseases, soon after her birth in 1982, she was admitted to the Neurosurgical Clinic in Visegradska Street in Belgrade where she was diagnosed with obstructive hydrocephalus. The Orbis-Sigma system for derivation of cerebrospinal liquor was implanted in order to decompress cerebral tissue and brainstem. She did not suffer any problems until she was 10 years of life. Tremors of the right hand, and soon of the left hand as well, accompanied by writing difficulties, appeared in February 1992. The difficulties progressed, so she was examined at the Neurosurgical Clinic in Novi Sad and diagnosed with internal hydrocephalus. Because of technical difficulties, magnetic resonance imaging (MRI) was done in Kaposvar (Hungary) in 1992, and it confirmed the diagnose of internal hydrocephalus. She was operated at the Neurosurgical Clinic

in Belgrade in July 1992. After the operation, the signs of papillary stasis receded and tremor disappeared completely. At the end of September, she received a punch in head in school, so she was checked at the Clinical Center in Novi Sad in October 1992 by the method of computed tomography (CT). Bilateral subdural blood collection and possible damage of previously implemented drainage shunt were recognized. Signs of increased intracranial pressure were noticed after the operation. The same month in 1992, the drainage system was revised in a way that the external drainage of liquor was replaced by Prudentz steady drainage system. After the operation, the patient could not speak and walk, and her eyeballs were turned right. She began walking exercises at the Rehabilitation Institute in Novi Sad. She walked shakily and had bad diction, but no headaches. EEG findings at that moment were pathological with epileptic activity. She took phenobarbitone a 0.1, 1x1 tablets per day until 1998.

Contrast-enhanced magnetic resonance imaging (MRI) was undertaken in 1998 at the Magnetic Resonance Imaging Center of the Clinical Center of Serbia in Belgrade. It showed the presence of cerebral tumor localized in lower thalamus and anterior parts of mesencephalon. Phenobarbitone tablets were withdrawn at that moment. She has periodical headaches since then, successfully treated with analgesics. The patient was explained that tumor is inoperable neurosurgically, so there was no surgery undertaken to remove it. At that time, skin changes accompanied by itching, described in objective medical report, began to develop. She had not been losing the bodyweight from the appearing of skin changes.

**Personal anamnesis.** The patient is a single, childless, pensioner. She lives in Zmajevu with her mother and brother. She suffered several head injuries: at the age of 4 she fell off the bicycle, and at the age of 5 a piece of concrete from a façade fell on her head. At the end of September 1992, she received a punch in the head and was operated at the Neurosurgical Clinic in Belgrade. As a child, she had mumps and two types of measles. She wore the Pavlik harness from 3<sup>rd</sup> to 9<sup>th</sup> month of her infancy. In 1989, she had her appendix taken out. She was regularly vaccinated. She did not have any allergic reactions. Family anamnesis Her paternal father had lung cancer. Her maternal mother is a cardiac patient and in the maternal line, there are several diabetic patients.

Arch Oncol 2007;16(3-4):81-3.

UDC: 612.82-006:616-008.6:616.594.1

DOI: 10.2298/A000804081S

<sup>1</sup>Clinic of Dermatovenerology, Clinical Center of Vojvodina, Novi Sad, Serbia,

<sup>2</sup>Clinic of Plastic and Reconstructive Surgery, Clinical Center of Vojvodina, Novi Sad, Serbia

Correspondence to:

Prof. Dr. Slobodan Stojanović,  
Clinic of Dermatovenerology, Clinical Center of Vojvodina, 1-9 Hajduk Veljko Street, 21000 Novi Sad, Serbia

[bobast@ptt.yu](mailto:bobast@ptt.yu)

## Abbreviations

Acanthosis nigricans = AN, Sign of Leser - Trelat = SLT, Magnetic Resonance Imaging = MRI, Computed Tomography = CT, Electroencephalography = EEG, No Abnormality Discovered = NAD,  $\beta$ -Human Chorionic Gonadotropin =  $\beta$ -HCG, PH finding = pathohistological finding, Paraneoplastic dermatose = PND, Central Nervous System = CNS, Polymerase Chain Reaction = PCR, Tablets = tbl.

Received: 23.09.2008

Provisionally accepted: 29.09.2008

Accepted: 16.10.2008

© 2008, Oncology Institute of Vojvodina, Sremska Kamenica

Dermatovenerological status In the neck region, armpits and groins, as well as in submammary fold, brown-gray to black velvet-like papillomatous regions of symmetrical distribution i.e. bilateral setting, was observed (Figures 1, 2). During an examination, numerous tumorous changes of papular appearance, colored from light brown to dark brown and black, of velvety surface and *fatty composition*, size 0.5-1 cm, which clinically match seborrheic keratoses, were observed, mostly on the skin of the trunk, back and face but on the other parts of skin as well (Figures 1, 2).



Figure 1. Patient with AN (neck) and SLT (seborrheic keratosis spread to the surrounding parts of the skin)



Figure 2. Patient with AN and SLT (multiple eruptive brown seborrheic keratoses on patient's back)

### LABORATORY AND OTHER FINDINGS

MRI findings from 1992 (Kaposvar, Hungary) showed sustained brain midline structures, enlarged I-II-III brain chamber, normal IV brain chamber and the aqueduct of Sylvius constricted. This aqueduct of Sylvius constriction is

regarded as congenital malformation, but at that time, there were not any expansive processes in cerebral tissue. Surgically implanted shunt was regular and functional. Extracerebral liquor space was symmetrical with normal volume.

Contrast-enhanced magnetic resonance imaging, undertaken in 1998 at the Magnetic Resonance Imaging Center, of the Clinical Center of Serbia, in Belgrade, showed the presence of tumefaction centrally and paracentrally located in lower thalamus and anterior parts of mesencephalon. Contrast-enhanced MRI findings pointed to glioma tumor i.e., astrocytoma (grade I-II i.e., low grade of malignity), which correspond with the typical MRI findings for this type of tumor (Picture 3). Tumor was neurosurgically inoperable and no surgery was undertaken.

According to Contrast-enhanced MRI findings from was done on June 25, 2008 (T1W sagittal, T2WFLAIR/DWI transversal and T2W coronal CT imaging of endocranium and postcontrast triplanar CT imaging of endocranium). Comparing these tomograms with previous contrast-enhanced MRI findings (from March 28, 2007), there were no changes in morphology and volume of clearly delineated spherical formation near the outgoing duct of III brain chamber to the right, with maximal diameter still 13 mm. The finding was unchanged: *Tu reg. mesencephali et thalami* (low-grade astrocytoma). There was no tumor expansion at present. Radiologist estimated the tumor expansion to be less than 1 mm in the last 10 years (1998-2008).

*Upper abdominal ultrasonography*: No abnormality discovered (NAD).

RTG of lungs: NAD.

*Tumor marker  $\beta$ -human chorionic gonadotropin ( $\beta$ -HCG)* (taken from liquor puncture performed at the Clinical Center of Serbia): Negative.

*Neurologist*: Normal findings

*Gynecologist*: Normal findings

*Endocrinologist*: Normal findings of the entire hormonal status

*Neurosurgeon*: Absence of internal hydrocephalus and cerebral tumor progression; tumor stage: T1 N0 M0.

*Plastic surgeon*: *Biopsio facta est*. A segment of skin was taken from the marked spot on laminated skin change on the neck. Brown tumor of hard composition, slightly hyperkeratotic surface and about the size of a grain of rice was excised from the skin of the right shoulder.

*Histopathological finding* (excisional biopsy skin sample of plaques changes on the neck), (18.9.2008.): DG: The histological finding indicates AN

*Histopathological finding* (excisional biopsy sample of tumorous changes on the skin of a right shoulder), (18.9.2008.): DG: *Keratosis seborrhoica cutis*. Other regular laboratory findings: NAD.

### DISCUSSION

Skin diseases of non-tumor nature caused by the presence of malignity of internal organs belong to the group of very heterogeneous paraneoplastic dermatoses (PND) (1,6-9). PND do not include metastases of malignant tumors of visceral organs in the skin or direct tumor metastases in the skin (1,6). These dermatoses are mainly characterized by complete or partial withdrawal after proper tumor treatment, i.e. after the regression of visceral malignity. The same dermatosis can appear again in the same patient with internal malignity, if the same tumor relapses or if the patient, possibly, suffers from tumor metastases in other organs. It is, also, typical of PND to be permanently associated with the tumor of internal organs, which corresponds to our case (1,6,7).

Pathogenesis of these dermatoses is not completely clarified, so they can be caused by some hormonal, allergic and autoimmune mechanisms or substances

that can originate from the tumor or the surrounding disintegrated tumor tissue. They can, also, be related to some genetic factors of the patient (1,6-10). In that effect, the most important for our case are the findings of the contrast-enhanced MRI evidencing the presence of central nervous system (CNS) tumor. Endocrinological disorders are not responsible for the appearance of AN (1,11). Some authors point out that beside a clear histopathological picture there is, also, a radiological difference between astrocytoma of low level of malignity (grade I-II), astrocytoma (grade III), and glioblastoma (grade IV), i.e. anaplastic glioblastoma (12). Astrocytoma and glioma comprise 80% of primary brain tumors (12,13). For technical reasons, a complete histopathological report, crucial in assessing the histological type of glioma, could not be done (14). Astrocytoma with low level of malignity usually appears between 20 and 40 years of age. Mutation and allelic losses on chromosomes 17p and 10p are primary genetic defects associated with astrocytoma and detected after molecular cytogenetic analyses. TP53 is the target gene on chromosome 17p and it is connected with 200 mutations in human tumors. Abnormalities of p53 gene can be important for tumor initiation and progression (14). Although in our case cytogenetic analyses were not done, congenital hydrocephalus (constricted aqueduct of Sylvius and consequential hydrocephalus) could indicate tumor's initiating genetic cause.

Paraneoplastic AN can, also, be associated with stomach, breast, gallbladder, lung and liver cancer and with lymphomas. It is considered an obligatory paraneoplastic dermatosis (1,2). Leser-Trelat syndrome (SLT), an optional paraneoplastic dermatosis (1), is proved in our case by sudden eruption of multiple seborrheic keratoses on skin and by pH monitoring findings of removed tumor. In some references, SLT and AN are described as concomitant paraneoplastic dermatoses of ovarian adenocarcinoma (15).

In case the detected cerebral tumor was metastatic, a routine  $\beta$ -HCG from liquor was done as differential diagnosis. Negative findings confirmed that the detected cerebral tumor was not metastatic (e.g., cervical planocellular carcinoma), but primary brain tumor. Tumor marker  $\beta$ -HCG can be used as evidence of potential cervical planocellular carcinoma and its metastases and dissemination (16).

In the end, we point out that special PCR (polymerase chain reaction) and immunohistochemical analyses have been developed recently for diagnostics and prognostics of glioma and, especially, glioblastoma (17).

## CONCLUSION

Clinical changes corresponded to paraneoplastic form of acanthosis nigricans.

Numerous skin tumors histopathologically matched seborrheic keratosis and reveal the clinical features of the sign of Leser-Trelat. It is interesting that in the same patient there were both, obligatory and optional, paraneoplastic dermatoses associated with malignant brain tumor. This PND continue permanently during the presence of internal tumors, respectively the primary brain tumor.

## Conflict of interest

We declare no conflicts of interest.

## REFERENCES

- Wolff H. Kutane Paraneoplasien. *Hautarzt*. Springer Verlag; 2001;52:159-72.
- Kaminska-Winciorek G, Brzezinska-Wcislo L, Lis-Swiety A, Krauze E. Paraneoplastic type of acanthosis nigricans in patient with hepatocellular carcinoma. *Adv Med Sci*. 2007;52:254-6.
- Moore RI, Devere TS. Epidermal manifestation of internal malignancy. *Dermatol Clin*. 2008;26(1):17-29.
- Barth G, Basten O, Ruchhoff J, Rompel R. Clinical and histopathological characteristics of early Leser – Trelat syndrome. *Hautarzt*. 2001;52(7):649-52.
- Vielhauer V, Herzinger T, Kortling HC. The sign of Leser – Trelat: a paraneoplastic cutaneous syndrome that facilitates early diagnosis of occult cancer. *Eur J Med Res*. 2000;5(12):512-6.
- Stojanović S, Poljački M, Dimoski A, Tasić S. Neke kliničko-epidemiološke odlike paraneoplastičkih dermatoza kod hospitalno lečenjih bolesnika na Dermatovenerološkoj Klinici u Novom Sadu. *Med Pregl*. 1995;48(2):44-7.
- Stone SP, Buescher LS. Life-threatening paraneoplastic cutaneous syndromes. *Clin Dermatol*. 2005;23(3):301-6.
- Weismann K. Skin disorders as markers of internal disease (Paraneoplastic dermatoses). *Ugeskr Laege*. 2000;162(50):6834-9.
- Kurzrock R, Cohen PR. Cutaneous paraneoplastic syndromes in solid tumors. *Am J Med*. 1995;99(6):662-71.
- Arao T, Obishi M, Yamada M, Nakamura T. Cutaneous –internal malignancy syndrome associated with specific skin lesions. *Gan To Kagaku Ryoho*. 1988;15(4 Pt 2-3):1581-7.
- Lučić Z, Hadnađev D, Govorčin M, Stojanović S et al. Najnoviji dijagnostički trendovi u radiologiji. *Med Pregl*. 2007;60(11-12):599-604.
- Orr B. Tumors of the nervous system. In: Spence RAJ, Johnston PG. *Oncology*. Oxford Medical Publications. Oxford University Press; 2001. p. 443-66.
- Figarella-Branger D, Collin C, Coulibalzi B, Quilchini B, Maues DPA, Fernandez C, Bouvier C. Histological and molecular classification of gliomas. *Rev Neurol*. 2008;164(6-7):505-15.
- Shapiro RW, Shapiro Rankin J, Walker, RW. Central Nervous System. In: Abeloff MD et al, editors. *Clinical Oncology*. 2<sup>nd</sup> ed. Churchill Livingstone; 2000. p. 1103-17.
- Kebrja MM, Belinson J, Kim R, Mekhail TM. Malignant acanthosis nigricans, tripe palms and the sign of Leser-Trelat, a hint to the diagnosis of early stage ovarian cancer: a case report and review of the literature. *Gynecol Oncol* 2006;101(2):353-5.
- Li D, Wen X, Ghali I, Al-Shalabi FM, Docherty SM, Purkis P, Iles RK. hCG beta expression by cervical squamous carcinoma – in vivo histological association with tumor invasion and apoptosis. *Histopathology*. 2008;53(2):147-55.
- Reddy SP, Britto R, Vinnakota K, Aparna H, Sreepathi HK, Thota B, et al. Novel glioblastoma markers with diagnostic and prognostic value identified through transcriptome analysis. *Clin Cancer Res*. 2008;14(10):2978-87