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Stroke-like symptoms in patient with scleromyxedema – case report

Objawy naśladujące udar mózgu u osoby z liszajem śluzowatym twardzinowym – opis przypadku

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Abstract

Scleromyxedema is a rare fibromucinous disorder also known as Arndt–Gottron disease. The diagnosis must fulfil the following criteria: generalised papular and sclerodermoid eruption, monoclonal gammopathy (mostly IgG, light lambda chains), no signs of thyroid disorders (differentiation with pretibial myxedema), and pathognomonic biopsy result (triad: mucin deposition, fibroblasts proliferation, fibrosis). In 60–90% of patients with scleromyxedema organs other than the skin are affected, and in 10–15% of patients the central nervous system may be involved. The aetiology of the disease still remains unclear. Currently, IVIg is considered the best therapeutic option. We present the case of a 64-year-old man with a 14-year history of scleromyxedema currently treated with intravenous immunoglobulins, in whom we observed episodes of transient aphasia, and aphasia with hemiparesis, with no radiological evidence of acute cerebral lesions. The patient was treated with rt-PA with initial good results. Dermato-neuro syndrome was considered as a cause of the patient's symptoms

Keywords: scleromyxedema, dermato-neuro syndrome, immunoglobulins

Streszczenie

Liszaj śluzowaty twardzinowy (*scleromyxedema*) jest rzadką przewlekłą chorobą zaliczaną do grupy mucynoz. Rozpoznanie ustala się, gdy spełnione są cztery kryteria: występowanie grudkowej liszajowatej wysypki skórnej o typowej lokalizacji, cechy liszaja śluzowatego twardzinowego w biopsji skóry (w tym gromadzenie mucyny w skórze, proliferacja wrzecionowatych fibroblastów i wzmożona synteza kolagenu), obecność monoklonalnej gammapatii we krwi obwodowej oraz brak dysfunkcji tarczycy. U 60–90% pacjentów występują dodatkowo objawy pozaskórne, w tym powikłania neurologiczne choroby, które pojawiają się u 10–15% z nich. Etiologia *scleromyxedema* jest nieznana, a terapią, która obecnie daje najlepsze efekty, są dożylne wlewy immunoglobulin (IVIg). W pracy przedstawiony został przypadek 64-letniego pacjenta z liszajem śluzowatym twardzinowym rozpoznanym 14 lat wcześniej, leczonym wlewami IVIg, który został przyjęty z powodu przemijającej afazji, a następnie afazji z niedowładem prawostronnym, leczonego trombolitycznie (mimo braku w neuroobrazowaniu zmian typowych dla niedokrwienia) z dobrym efektem.

Słowa kluczowe: liszaj śluzowaty twardzinowy, objawy skórno-neurologiczne, immunoglobuliny

CASE REPORT

A 64-year-old man was admitted to the neurological department with motor aphasia of unknown time of onset – the symptom was present while awaking (wake up stroke). A neurological examination performed on admission found resolving motor aphasia. Brain computed tomography (CT) and diffusion-weighted magnetic resonance imaging (DW-MRI) were performed, and acute ischaemic lesions were excluded. As speech disorder remitted soon after the admission, thrombolytic therapy was not initiated.

Medical history revealed that the patient suffered from scleromyxedema which was diagnosed 14 years earlier, and has been treated with intravenous immunoglobulins (IVIg; the last dose of IVIg was given 9 weeks before admission, the next dose was delayed due to the lack of IVIg). Transient ischaemic attack (TIA) with aphasia a year back (also when IVIg treatment was delayed), stenosis of the left internal carotid artery (LICA), hypertension, hyperuricaemia, focal epilepsy (treated with valproic acid), Raynaud syndrome, and immunoglobulin G (IgG) gammopathy were also present in medical history. In addition, the patient underwent cervical and lumbar spine surgery for spinal disc herniation.

Standard diagnostic procedures were introduced. The presence of 60% LICA stenosis on CT angiography was confirmed, and significant dysrhythmias were excluded on Holter electrocardiography. Dyslipidaemia and hyperglycaemic disorders were not found. Acetylsalicylic acid was introduced for secondary prevention of cerebrovascular events.

On the fourth day of hospitalisation, motor aphasia recurred with blood pressure elevation and psychomotor agitation (NIHSS – National Institutes of Health Stroke Scale – score 2). No acute lesion was found on brain CT scan, so thrombolytic therapy was given with total resolution of aphasia (NIHSS score 0). Unfortunately, a few hours later speech disorders and right-sided hemiparesis appeared (NIHSS score 8). A follow-up brain CT and DW-MRI were still normal (Fig. 1, Fig. 2 A, B).

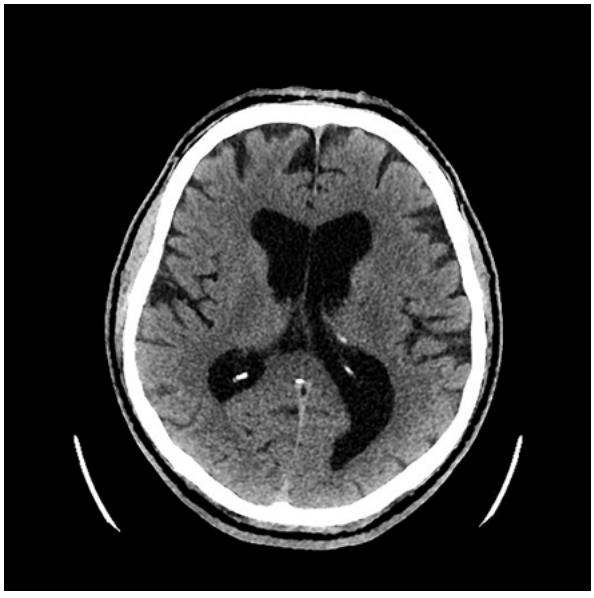

Fig. 1. Brain CT performed after the recurrence of aphasia and onset of right-sided paresis revealed no ischaemic lesions

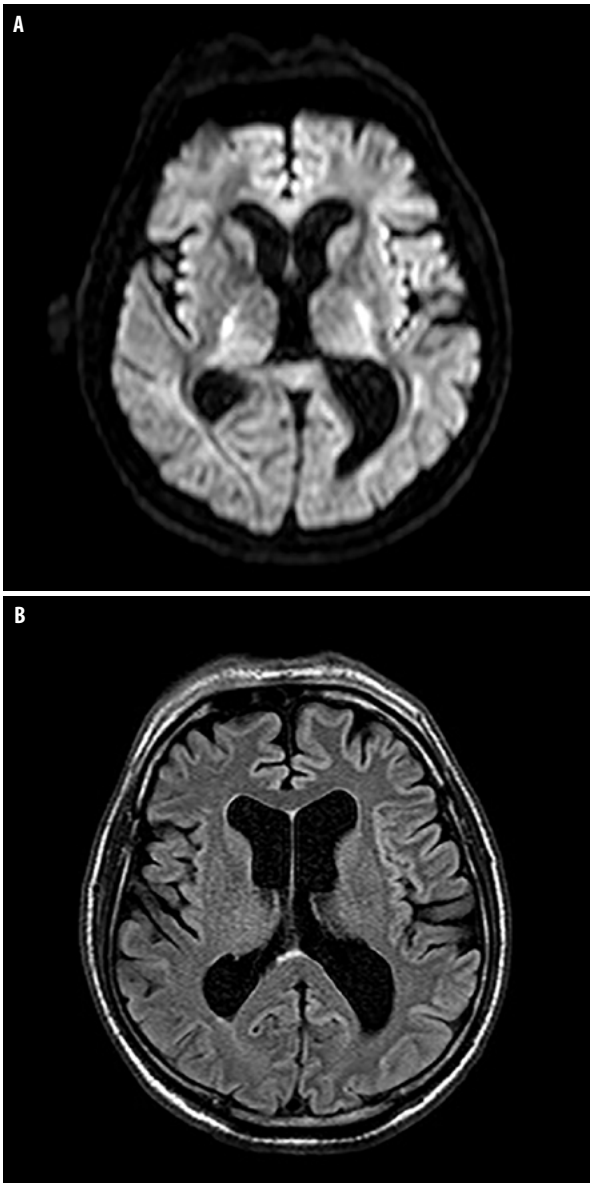

*Fig. 2. Brain MRI with DWI sequence performed after the recurrence of aphasia and onset of right-sided paresis revealed no marked hyperintensity on DWI (**A**) or reduced ADC values. Also, no ischaemic lesions were found in the FLAIR sequence (**B**)*

Because of inconsistent clinical and radiological findings electroencephalography (EEG) was performed, revealing inter-hemispheric asymmetry in cortical activity with left hemisphere suppression of all frequencies (Fig. 3). Todd's paresis was suspected, so anti-epileptic pharmacotherapy was intensified (levetiracetam was added to valproic acid), but without improvement. Lumbar puncture was also performed, but no signs of inflammation in the cerebrospinal fluid (CSF) were found, and the protein level was normal.

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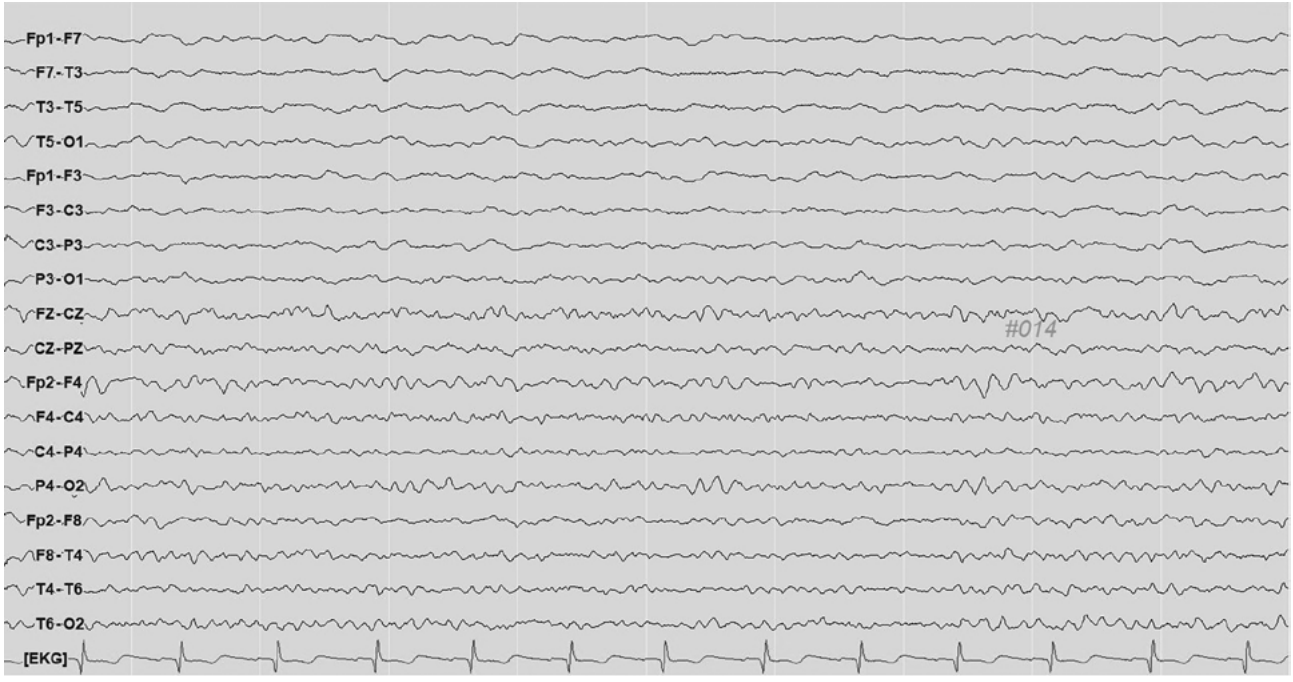

Fig. 3. EEG revealed inter-hemispheric asymmetry in cortical activity with left hemisphere suppression of all frequencies

The patient's condition deteriorated: dysphagia developed, and scleromyxedema worsened with generalised skin hardening, which made mouth opening and chest expansion difficult, and even intubation was impossible. As a result, the patient developed respiratory failure and required emergency tracheotomy and respiratory therapy. A nasogastric tube was also necessary to provide appropriate nutrition, administer medication, and prevent choking.

As skin symptoms deteriorated concomitantly with neurological symptoms, IVIg treatment was introduced at a dose of 0.4 g/kg/24 h for 5 consecutive days, which caused clinical improvement: aphasia and right-sided paresis remitted, and generalised skin hardening resolved, but dysphagia was still a problem, so percutaneous endoscopic gastrostomy was performed.

After a few days of IVIg treatment, left-sided hemiparesis was noted (with no ischaemic or haemorrhagic lesions seen on brain CT), but due to recent thrombolytic and IVIg therapy no further pharmacological measures were introduced. Respiratory and motor rehabilitation was continued.

The patient was discharged to the rheumatology department for further care. On discharge, he was in a good general condition. The speech function was disturbed by the presence of a tracheostomy tube, but despite that the communication was normal. Mild paresis of the left upper limb was present. Assisted feeding was in progress.

In conclusion, stroke was diagnosed, and scleromyxedema was recognised as the main cause of cerebral ischaemia, so thrombolytic and IVIg therapies were introduced. The patient requires regular IVIg administration for the prevention of cerebrovascular incidents.

DISCUSSION

Scleromyxedema is a rare (its exact prevalence and incidence are unknown) chronic mucinosis with systemic involvement (its more localised, dermal, less severe form is known as myxedematosus or papular mucinosis). It affects both men and women in the age range of 30 to 70 years, and it is associated with poor prognosis if cardiovascular or pulmonary systems are involved.

The aetiology of the disease is unknown, but increased mucin (produced by fibroblasts) deposition in the skin and subcutaneous tissue leads to the formation of lichenoid papules, and thickening and hardening of involved tissues (Serdar et al., 2010). Excessive hyaluronic acid and prostaglandin E production by fibroblasts and glycosaminoglycan synthesis is also observed in scleromyxedema patients (Yaron et al., 1985).

Most patients with scleromyxedema have a monoclonal paraprotein band (usually of IgG light lambda chains), but the association between this paraprotein and mucin deposition is not clear. Moreover, the paraprotein level does not correlate with disease severity, progression or response to therapy, and a monoclonal paraprotein band is present even in patients with disease remission. Nevertheless, this gammopathy requires patient follow-up, as monoclonal gammopathy may transform into myeloma multiplex. Therefore, scleromyxedema may be recognised as a paraneoplastic syndrome (Olasiński, 2016; Terlikowska-Brzósko et al., 2010).

The diagnosis of scleromyxedema is based upon the following criteria: 1) generalised papular and sclerodermoid eruption is present, 2) triad of histological features is found

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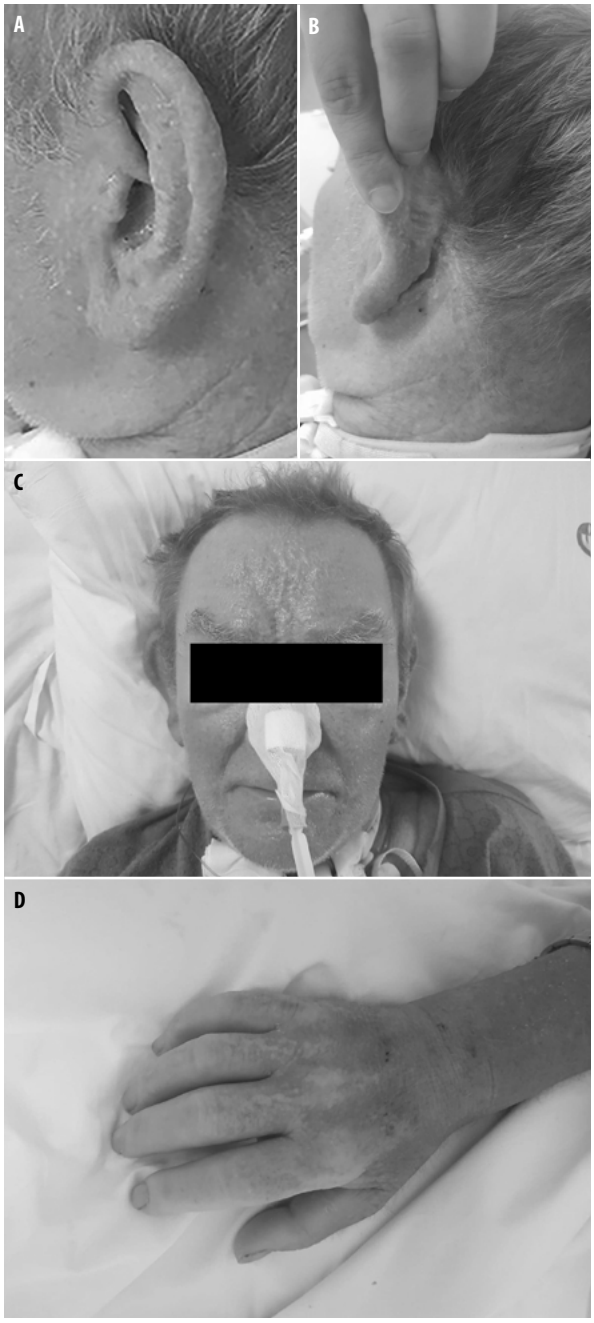

*Fig. 4. Localised lichenoid papules and urticarial plaques and nodular eruptions around the auricles (**A**, **B**) and face (**C**). Sclerodactylia (**D**)*

in skin biopsy (diffuse mucin deposition, fibroblast proliferation, fibrosis), 3) monoclonal gammopathy is present, and 4) no thyroid disorder is found.

As far as the clinical presentation is concerned, most patients have skin changes such as localised or generalised lichenoid papules and urticarial plaques, and nodular eruptions around the auricles, on the dorsal hands, face or extensor surfaces of the arms and legs (Fig. 4 A–D). The facial ridges and facial folds may be also distorted. The progression of skin lesions eventually leads to decreased mobility of the face (microstomia), fingers (sclerodactylia), and extremities. If internal systems are affected, restrictive and obstructive lung disease, pulmonary hypertension, renal insufficiency and cardiovascular abnormalities (myocardial infarction, hypertension, atherosclerosis) may develop. Severe proximal muscle weakness, inflammatory myopathy, seronegative polyarthritis, migrating arthritis, corneal deposits, thinning of the eyelid and ectropion have also been reported (Koronowska et al., 2013; Marshall et al., 2010; Sala et al., 2016). Dysphagia is the most common gastrointestinal manifestation resulting from oesophageal dysmotility (Sala et al., 2016). Central nervous system involvement (known as dermato-neuro syndrome) is rare, and leads to diverse clinical manifestations including encephalopathy, convulsions, coma or focal signs as a result of transient ischaemic attack or stroke (Fleming et al., 2012). The classical triad of symptoms in dermato-neuro syndrome involves fever, coma, and convulsions following flu-like prodrome symptoms.

The mechanisms of systemic involvement in scleromyxedema patients are as enigmatic as the aetiology of its skin manifestations. Mucin deposition is rarely found within blood vessels or perivascular connective tissue of affected organs (Fleming et al., 2012, Godby et al., 1998; McCuistion and Schoch, 1956), but some authors report the presence of mucin deposition in the myocardium and coronary arteries in patients with cardiovascular system involvement. In dermato-neuro syndrome, the role of paraprotein in increasing blood viscosity or leukocyte aggregation or IgG transition through brain-blood barrier mediated by increased interleukin 6 (IL-6) production have been suggested. Fleming et al. (2012) reviewed 19 cases of dermato-neuro syndrome in the age range of 30 to 67 years. Most patients presented with confusion, seizure and coma preceded by flu-like symptoms (with fever) or gastrointestinal manifestations (nausea). Just a few had focal symptoms such as dysarthria, hemiparesis or pyramidal signs. In nearly all cases, the findings of brain CT scans or brain magnetic resonance imaging were normal. EEG results varied from nonspecific changes via encephalopathic changes to diffuse slowing, epileptiform discharges, focal epileptic activity or status epilepticus. CSF examination revealed increased protein levels in most cases. Interestingly, central nervous system (CNS) symptoms appeared within the initial 4 years of the onset of skin disease in all patients. Nevertheless, Charles et al. (2014) reported a case of a 57-year-old woman with 14-year history of scleromyxedema and dermato-neuro syndrome. In Fleming's review, 32% of patients had recurrent episodes, and 32% of them died during their acute neurologic disorders (Fleming et al., 2012).

Despite some common signs and symptoms of dermato-neuro syndrome reported, usually involving altered consciousness, the diagnosis is still made by excluding other causes of patients' clinical presentation. Karaman et al. (2015) suggest that all patients with a history of scleromyxedema diagnosed with altered consciousness or other

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neurological deficits that cannot be explained by another disease should be considered as having dermato-neuro syndrome.

Various therapeutic approaches have been introduced in patients with scleromyxedema and dermato-neuro syndrome, including different immunosuppressive therapies (alone or in combination therapy), such as intravenous immunoglobulin (IVIg) as the most commonly selected therapeutic choice, systemic glucocorticoids, plasmapheresis, cyclophosphamide, melphalan or bortezomib (Fett et al., 2011; Gholam et al., 2007; Rey and Luria, 2009). Nevertheless, spontaneous improvement has also been reported (Fleming et al., 2012). The outcome of treatment is always uncertain, with possible complete or partial neurological recovery, though fatal outcome is not uncommon, either (Fleming et al., 2012).

Our patient did not have the classic triad of dermato-neuro syndrome. The neurological manifestation of the disease mimicked acute stroke, and acute stroke management according to the current guidelines resulted in transient improvement. However, further diagnostic tests performed after neurologic and systemic deterioration did not reveal acute ischaemic brain damage. Moreover, other acute CNS disorders manifesting with focal symptoms were excluded, and clinical improvement was eventually achieved with IVIg treatment for scleromyxedema.

Although the patient's concomitant diseases, especially significant LICA stenosis, might increase the risk of cerebrovascular incident, we believe that in the case of a typical ischaemic stroke with symptoms as severe as in our patient, we should have found the signs of ischaemic brain damage. The history of scleromyxedema, atypical clinical presentation (neurological deterioration combined with severe exacerbation of scleromyxedema symptoms), the lack of ischaemic damage in neuroimaging, and neurological improvement after IVIg treatment, might suggest that the case may involve atypical dermato-neuro syndrome.

Both neurological incidents – TIA a year before and stroke-like symptoms during the last hospitalisation – appeared when IVIg treatment was discontinued because of shortage of the drug. The patient recovered nearly completely after undertaking regular IVIg therapy (the speech disorder and dysphagia resolved, and only mild left upper limb paresis is still present).

The above findings may be evidence for the efficacy of IVIg treatment in scleromyxedema patients.

Conflict of interest

Authors do not report any financial or personal connections with other persons or organisations, which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

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