To the Editor,

A 63-year-old man presented with acute-onset weakness in his right limbs and global aphasia on April 19, 2015. He had hypertension and hyperlipidemia for 10 years and had received percutaneous coronary intervention twice in this hospital in the past 5 years. At the emergency room, brain computed tomography revealed diffuse cortical atrophy, hydrocephalus, and low-attenuation changes in bilateral periventricular regions. The patient was admitted under a tentative diagnosis of left middle cerebral artery territorial infarction. His medical history revealed that he had suffered several ischemic attacks in the past 10 years. He had an ischemic stroke with global aphasia in June 2006 with fair recovery. Unsteady gait and slurred speech were noted in March 2010, followed by coarse hand tremor and paresthesia of the left lower limb in November 2010. A brain computed tomography performed in that year revealed leukoaraiosis and diffuse cortical atrophy. In addition, several episodes of blurred vision in his left visual field, each lasting for < 30 minutes, occurred in July 2011. Finally, delirium was noted in July 2013, and dementia was diagnosed in August 2013. The patient’s eldest brother also had stroke and dementia.

During hospitalization, magnetic resonance imaging (MRI) of the brain was performed that revealed leukoaraiosis and high signal intensities in bilateral anterior temporal lobes on fluid attenuation inversion recovery and T2-weighted images. Owing to a high suspicion of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), a dermatologist was consulted for skin biopsy. The skin biopsy specimen was obtained from normal-appearing forearm skin. The pathology showed solar elastosis and mild dermal perivascular lymphocytic infiltrate. The vessels were unremarkable under microscopic examination. Electron microscopy revealed granular osmiophilic material (GOM) deposition in the vascular smooth muscle cells of the small arterioles (Figure 1A). The deposits were located near the basal lamina and were present in the cytoplasm as pseudoinclusions (Figure 1B). These findings are consistent with CADASIL.

Figure 1

Electron microscopy showing granular osmiophilic material (white arrow) within (A) vascular smooth muscle cells in the small arteriole and (B) the cytoplasm, presenting as pseudoinclusions (A, 20,000×; B, 40,000×).

Conflicts of interest: The authors declare that they have no financial or non-financial conflicts of interest related to the subject matter or materials discussed in this article.

http://dx.doi.org/10.1016/j.dsi.2016.09.006

Please cite this article in press as: Chang R-S, et al. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy diagnosed from skin biopsy, Dermatologica Sinica (2016), http://dx.doi.org/10.1016/j.dsi.2016.09.006
CADASIL was initially recognized in 1977 and was known as a cerebrovascular disease characterized by migraines, recurrent ischemic strokes, and dementia in middle-aged adults.\(^1\) Mutation in chromosome 19q12 was found in 1993, and point mutations in \(\text{NOTCH3}\) was identified in 1996.\(^2\)

Patients usually develop migraines as the first symptom of CADASIL in their 3\(^{rd}\) decade of life. Recurrent subcortical ischemic events subsequently occur during middle age. The repeated stroke attacks finally lead to early-onset dementia at about 50–60 years of age. A study in Chinese individuals revealed that the incidence of migraine in CADASIL patients was much lower (5%) in Chinese individuals compared with the Western population (20–40%).\(^3\)

The typical findings in an MRI include increased signal on T2-weighted images over the external capsule and anterior part of the temporal lobes. The sensitivity and specificity of MRI for the diagnosis of CADASIL were 89% and 86%, respectively.\(^4\) However, a recent study in Taiwan found that high signal intensities in the anterior temporal lobe in T2-weighted MRI scans may not serve as a sensitive diagnostic sign for CADASIL in Chinese individuals.\(^5\)

Brain biopsy has historically been the only method for the diagnosis of CADASIL. However, GOM was found in the vessel wall of arteriole in the skin of CADASIL patient in 1994.\(^6\) Since then, CADASIL has not been considered a purely neurologic disease, but a systemic disease and can be diagnosed through a simple skin biopsy from a normal-appearing skin. Skin biopsy is a safer and more feasible diagnostic tool. Under electron microscopy, the presence of GOM in the basement membrane of vascular smooth muscle cells in the dermal arteriole is pathognomonic. Sometimes, GOM presented as cytoplasmic pseudo-inclusions in CADASIL. The sensitivity and specificity of GOM for the diagnosis of CADASIL is nearly 100%, whereas the sensitivity is variable.\(^7\) A recent study suggested that the skin biopsy specimen should include the border zone between the deep dermis and upper subcutis, where medium or small arterioles will be found and GOM can be best detected.\(^8\)

Although genetic testing for \(\text{NOTCH3}\) may have a better sensitivity and high specificity, it is not available in every institution and our patient did not agree to undergo this test because of the cost. Skin biopsy remains a good cost-effective diagnostic tool for CADASIL.

In conclusion, we presented a case of CADASIL diagnosed by a typical electron microscopic finding of GOM in the basement membrane of vascular smooth muscle cells. Besides the genetic test for the mutations in \(\text{NOTCH3}\), dermatologists could play an important role in diagnosis by performing a simple punch biopsy for electron microscopic examination.

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Received: Jun 30, 2016
Revised: Aug 29, 2016
Accepted: Oct 1, 2016