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Systemic Histopathology And Calcium Chemical Composition In Extracutaneous Tissues From A Uremic Calciphylaxis Patient Who Underwent Long-term Treatment With Human Amnion-derived Mesenchymal Stem Cells

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Background

Calciphylaxis is a rare and highly fatal disease that manifests with calcification and thrombosis of microvessels, ischemia and necrosis in the skin and subcutaneous tissues. Whether it is a systemic process is unknown. We have proposed that human amnion-derived mesenchymal stem cells(hAMSCs) are a promising therapy for uremic calciphylaxis, also known as calcific uremic arteriolopathy (CUA). However, the histopathological features and chemical composition of extracutaneous tissues remian unclear.

Methods

A female CUA patient was treated with intravenous and local hAMSCs. She gradually developed regenerative skin tissues, however, she passed away due to a post-stroke intracerebral hemorrhage after 20 months. Her body was donated for medical research. Her extracutaneous tissues were compared with those of end-stage kidney disease (ESKD) patients(n=7). We conducted histopathological analysis on multiple tissues, including the brain, heart, cardiac valve, coronary artery, lungs, kidneys, liver, spleen, pancreas, uterus, and ovary. Raman spectroscopy and imaging were applied to identify the components and morphology of calcification. The distribution of transplanted hAMSCs, derived from the amnion of male fetus, in multiple tissues of the female CUA patient was determined by detecting the human Y chromosome using RT-PCR.

Results

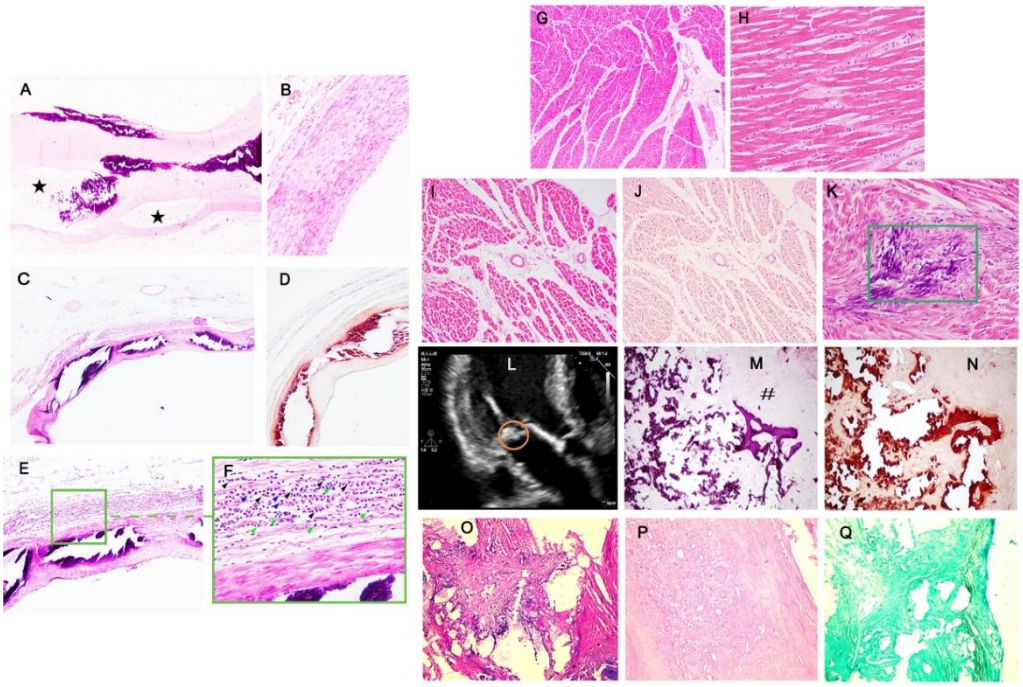

Figure 1. Comparison of the cardiovascular system in ESKD patients and the calciphylaxis patient treated with hAMSCs.
(A-B) ESKD patients (H&E). (A) Coronary atherosclerosis is characterized by unevenly thickened artery wall, fibrous hyperplasia, calcium deposition within the atheromatous plaque (40 ×). (B) Thickened artery wall and no inflammatory cell infiltration in the adventitia of the coronary artery wall (200 ×). (C-F) The calciphylaxis patient. (C) Diffuse medial circumferential calcification, fibrous intimal hyperplasia, and unevenly thickened artery wall (H&E, 40 ×). (D) Medial circumferential calcification of the coronary artery wall (Alizarin Red, 40 ×). (E) Diffuse inflammatory cell infiltration (H&E, 200 ×). (F) Lymphocytes, macrophages, and eosinophils in the adventitia of the coronary artery wall (H&E, 400 ×).
(G-H) An ESKD patient (H&E). Normal histological structure (G, 40 ×) and slight fibrous hyperplasia within cardiomyocytes (H, 200 ×). (I-K) The calciphylaxis patient. (I) Marked fibrous hyperplasia within cardiomyocytes (H&E, 40 ×). (J) No obvious calcification within cardiomyocytes (Alizarin Red, 40 ×). (K) Suspected scattered calcification loci and fibrous hyperplasia within cardiomyocytes (H&E, 200 ×).
(L-Q) The calciphylaxis patient. (L) Representative images of cardiac valve calcification by echocardiography, with the circle indicating the calcification of the posterior annulus of the mitral valve. (M) Mitral annular mucus degeneration, fibrous hyperplasia, calcification, and destroyed valve (H&E, 40 ×). (N) Mitral annular calcification (Alizarin Red, 40 ×). (O-Q) Mitral valve (40 ×). No inflammatory cell infiltration (O, H&E). No obvious colonies and hyphae (O, H&E; P, Periodic Acid-Schiff). No bacteria, fungi, granulomas, and pneumocystis (Q, Grocott's Methenamine Silver).

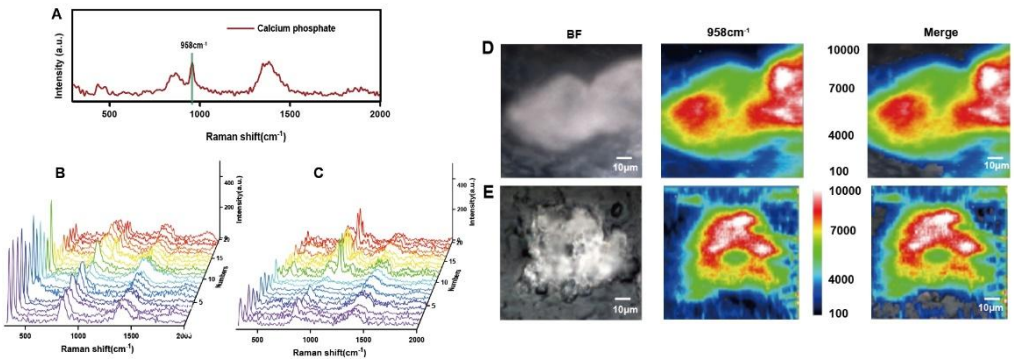

Figure 2. Raman mapping of calcium deposition in the calciphylaxis patient treated with hAMSCs.
(A) Raman spectral data corresponding to calcium phosphate (958 cm^{-1}) in the mitral valve and kidney tissue. (B) Raman spectra of 20 random calcium depositions in the mitral valve tissues. (C) Raman spectra of 20 random calcium depositions in the kidney tissues. (D) Raman mapping of calcium phosphate in the mitral valve (1000 ×). (E) Raman mapping of calcium phosphate in the kidney tissue (1000 ×).

Conclusions

Our findings shed light on a better understanding of extracutaneous tissue injuries in CUA patient. Although the skin regenerated after hAMSC treatment, microvascular lesions still exist in multiple tissues. In the future, it will be necessary to explore blood biomarkers to guide personalized hAMSC treatment strategies for calciphylaxis patients. This will help protect internal organs more safely, economically, and effectively.