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Therapy effects of green tea in a patient with systemic light-chain amyloidosis

Sirs: Green tea (*Camellia sinensis*) has been credited as a health promoting substance with ubiquitous properties, many of which have not yet been validated by scientific evidence. Experimental proof of the ability of one green tea polyphenol, (−)-epigallocatechin-3-gallate (EGCG), to induce apoptotic cell death in leukemic B-cells, or reduce cerebral amyloidosis in Alzheimer transgenic mice through modulation of amyloid precursor protein cleavage were reported previously [14, 13]. In vitro experiments have shown that EGCG very efficiently prevents amyloidogenesis, as well as exhibits unusual and powerful protein remodeling activity. It recognizes soluble as well as insoluble amyloidogenic structures and actively induces the formation of benign aggregation products, that do not polymerize into fibrils [2]. Proof of clinical benefit, possible toxicities, or knowledge of optimal dosage is still lacking. We describe a patient with systemic light-chain (AL) amyloidosis who showed impressive cardiac and clinical improvement after therapy with daily ingestion of green tea.

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Case report

A 76-year-old male patient presented to our hospital with a history of dizziness and progressive fatigue. He reported no previous history of cardiac decompensations. The physical examination showed an enlarged tongue, a mild pedal edema, a small unilateral suborbital purpura and was otherwise within normal limits. Low voltage on 12-lead electrocardiography was not present on ECG, but a trifascicular heart block. Proteinuria (6 g/day), hypoalbuminemia (2.8 g/dl) and hemorrhagic diathesis due to diminished coagulation factors IX and X were present. Monoclonal serum and urine light chain immunoglobulin with an abnormal κ:λ ratio was also demonstrated (Table 1). Diagnosis of AL amyloidosis was confirmed with biopsy of a hyperplastic colonic polyp.

A comprehensive echocardiographic and strain imaging examination showed abnormal myocardial texture, with punctiform increase of echogenicity ("granular sparkling") and asymmetric hypertrophy of the left ventricular septum, with impaired left ventricular systolic and diastolic function, as well as reduced longitudinal myocardial deformation (Table 1).

A DDD-pacing pacemaker was implanted in February 2005 and therapy with melphalan and high-dose dexamethasone was initiated and conducted during 14 months until completion in August 2006, resulting in the stabilization of echocardiographic parameters. No further medication was prescribed. In the meantime, the patient, an emeritus professor for internal medicine and hematology of our university, was informed by former members of his staff about the results of promising in vitro experiments with EGCG [2]. Because commercially existing EGCG, an odorless water

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Table 1 Course of clinical, laboratory and echocardiography parameters

Parameters	At diagnosis	After 14 months chemotherapy	After 11 months green tea
Clinical			
NYHA class	III–IV	III–IV	II
6MWT (m)	433	472	689
EQ-5D, score	0.62	0.62	1.00
EQ-VAS (%)	25	25	85
Laboratory			
λ-light chain (mg/l)	73	44	38
κ-light chain (mg/l)	21	19	21
κ/λ ratio	0.29	0.43	0.56
Quick time (%)	68	77	96
PTT (s)	48	37	28
Urea (mg/dl)	61	83	78
Creatinine (mg/dl)	2.02	2.39	2.66
Echocardiography			
Septum (mm)	16.5	16.5	12.6
LV mass (g)	303.5	302.8	240.7
LA (mm)	48	47	42
LV-EDD (mm)	52	53	52
LV-EF (%)	37	38	42
Strain (−%)	7	7	12
Strain rate (1/s)	0.8	0.8	1
PASP (mmHg)	40	38	25
LV-EDP (mmHg)	25	23	14

NYHA New York Heart Association functional classification, *6MWT* 6-minute walk test, EQ-5D: *EuroQol-5D* Euro-Quality-of-Life five dimensions quality of life questionnaire, *EQ-VAS EuroQol-VAS* Euro-Quality-of-Life visual analog scale, *PTT* partial thromboplastine time, *LV mass* left ventricular mass as calculated with the Devereux equation, *LA* left atrium, *LV-EDD* left ventricular end diastolic diameter, *LV-EF* left ventricular ejection fraction as calculated with the modified Simpson's rule, Strain: longitudinal myocardial deformation, *SR* strain rate, values given are for diastolic myocardial deformation rate, *PASP* pulmonary artery systolic pressure as estimated through tricuspid regurgitation velocities plus right atrial pressure, *LV-EDP* left ventricular end diastolic pressure as estimated with the Nagueh formula [(1,24*E/Ea)+1,9]

soluble white powder, is only available for animal trials, he started to drink one and half to two liters of green tea daily in order to allow a substantial biodisponibility of the potentially helpful "new therapy" [5].

Progressive clinical recovery with improvement in quality of life, normalization of hemorrhagic diathesis and stable, however impaired renal function (Table 1), as well as enhancement of echocardiographic parameters could be observed through 11 months of therapy with EGCG via green tea infusions. Septal hypertrophy showed a significant reduction. In addition, longitudinal myocardial deformation of left ventricular septum, which was severely diminished before, showed considerable improvement after therapy (see, Fig. 1).

Discussion

Systemic amyloidosis is a devastating disease with limited, sometimes frustrating treatment options [12]. Heart involvement is the major prognostic determinant in systemic amyloidosis and can be easily assessed by echocardiography [4, 6, 15], allowing non-invasive diagnosis and follow-up examinations. Cardiac magnetic resonance imaging and endomyocardial biopsy complete the diagnostic algorithm. However, echocardiographic parameters alone lead to the diagnosis of cardiac involvement, in the presence of clinical and laboratory evidence in a patient with a positive result of a noncardiac biopsy [4]. Cardiac response to therapy is considered established when mean interventricular septal thickness decreases by 2 mm. However, even patients with complete hematologic response and improvement in other organs have little changes in wall thickness. Therefore, surrogate parameters such as improvement in NYHA functional class or left ventricle ejection fraction are proposed [4]. A mean interventricular septal thickness reduction of 3.9 mm in our case and improvement in longitudinal left ventricular function, along with increase in 6-min walking distance and significant increment of quality of life parameters are seen as proof of response by means of a daily treatment based on the oral administration of EGCG from green tea.

Possible mechanisms of actions of EGCG and other green tea catechins are not fully understood, and might include activation of tissue metalloproteinases [9] and/or the capability of inducing the formation of benign aggregation products from soluble and insoluble amyloidogenic structures [2]. In vitro experiments have shown that EGCG inhibits fibrillogenesis by converting fibrils into highly stable, non-toxic spherical oligomers, thus preventing their polymerization. EGCG also remodels preformed amyloid fibrils into non-toxic amorphous protein aggregates, probably allowing their withdrawal from intercellular space [2]. The possibility of a late response to the foregoing chemotherapy is highly unlikely, considering the overall course of this particular case. Furthermore, no cases on late response to chemotherapy in AL amyloidosis, especially concerning left ventricular hypertrophy, have been reported so far.

EGCG content in green tea infusions may differ greatly depending on the method of preparation [3]. Furthermore, EGCG is unstable under physiologic conditions and could be rapidly degraded or metabolized, showing poor bioavailability, an important issue when translating in vitro activities into in vivo animal and human studies [3]. Alternative delivery methods [7] and/or chemical conversions will be needed to overcome this problem [8, 16].

Current treatment of systemic amyloidosis includes three approaches. The first one interferes with the production of the precursor protein; the second focuses on stabilizing its native structure, thus preventing its transition into a misfolded protein, and the

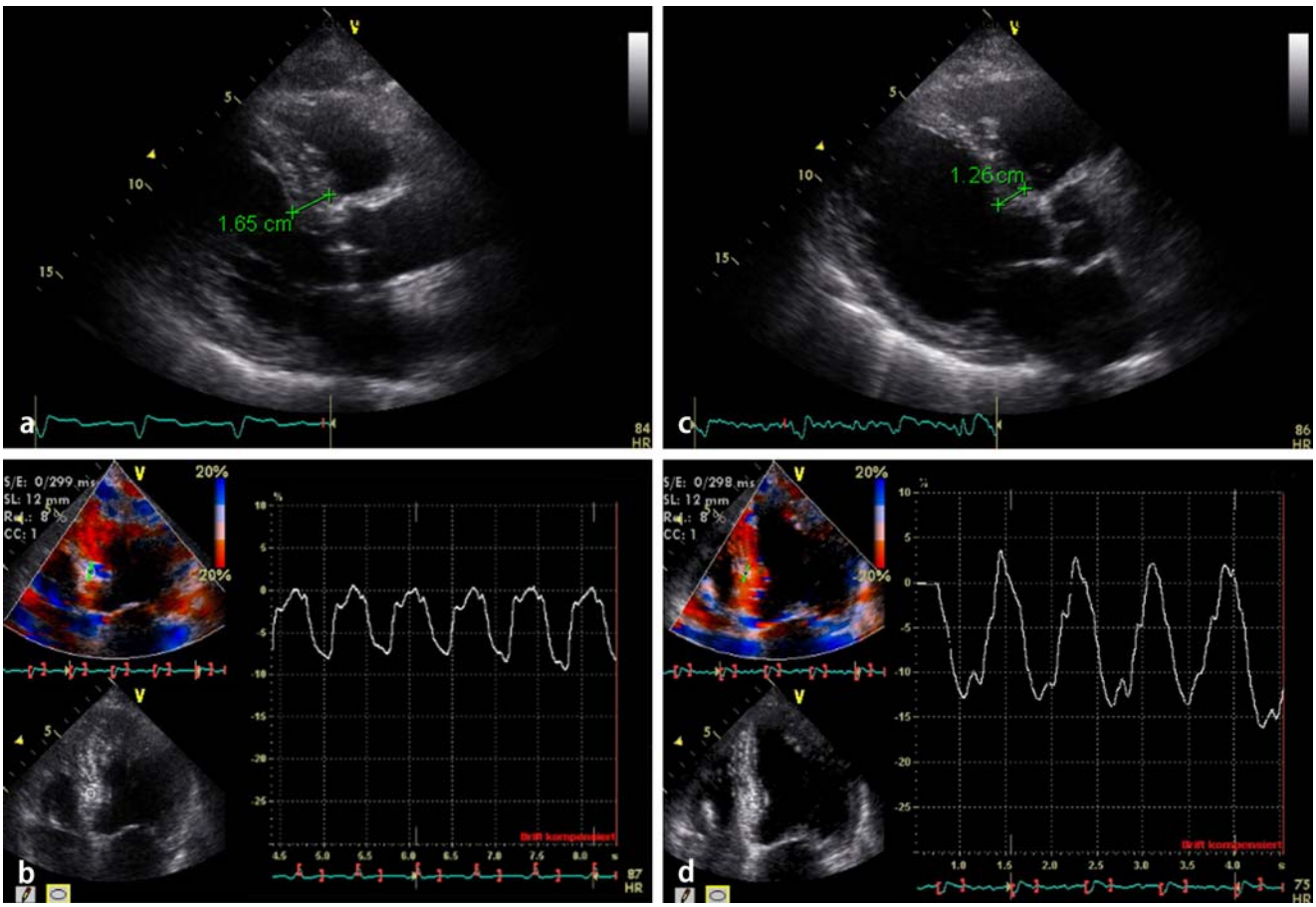

Fig. 1 Parasternal long axis view with measurements of end-diastolic basal septum (panel **a**) and longitudinal strain as obtained from the apical four chamber view (panel **b**) before therapy. After therapy, an evident decrease in left ventricle septal thickness (panel **c**) and increase in longitudinal myocardial deformation (panel **d**) can be observed

third targets amyloid deposits directly, by destabilizing amyloid fibrils so that they can no longer maintain their β-pleated sheet configuration [12]. Studies have shown the therapeutic potential of two drugs in the last group, a compound that binds serum amyloid P component [10] and eprodisate [1]. EGCG might constitute a new drug targeting tissular deposits of amyloid fibrils. In patients without contraindications for the procedure, heart transplantation is the last therapeutic chance in cases of advanced cardiac involvement with severe systolic and diastolic dysfunction [11].

This is the first report on in vivo effects of EGCG from green tea on quality of life, functional capacity and especially on cardiac morphology and function in a patient with systemic light-chain amyloidosis. Prospective, double-blind, randomized and placebo controlled clinical studies will be necessary to prove clinical benefit, possible toxicities and dosage of EGCG in the therapy of AL amyloidosis.

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