



Acute right heart failure in Waldenström macroglobulinemia: A case report

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Abstract

Waldenström macroglobulinemia (WM) is a low-grade B-cell clonal disorder with lymphoplasmacytic bone marrow involvement and monoclonal immunoglobulin M (IgM) with poor prognosis. Clinical features include anemia, thrombocytopenia, hepatosplenomegaly, lymphadenopathy and hyperviscosity. We report the case of a 42-year-old male who presented with unexplained weight loss. The diagnosis of WM was established after morphological and immunohistochemical examination of the patient's bone marrow along with an elevated serum IgM level. He started chemotherapy with cyclophosphamide, bortezomib, dexamethasone and, four months later, rituximab was added. Five months later the patient presented with relapse of the hematological disease, hyperviscosity syndrome and acute right heart failure. Echocardiography showed a dilated right ventricle with decreased global systolic function and severe systolic pulmonary artery pressure, with normal left cardiac function and volumes. Despite maximal medical therapy, the patient died in day six of hospitalization. This case is distinguished by the rapidly evolving rare haematological cancer despite optimal chemotherapy and a multidisciplinary approach associated with chemotherapy-related late right heart dysfunction in a young man, without any cardiovascular risk factors or previous myocardial disease.

Keywords

Waldenström macroglobulinemia (WM), hyperviscosity syndrome, right heart failure, pulmonary hypertension, cardiotoxicity.

Abstract

Macroglobulinemia Waldenström (MW) este o malignitate clonală cu grad scăzut de diferențiere histologică a limfoplasmocitelor medulare de tip B, cu producție de imunoglobuline M (IgM), având un prognostic rezervat. Manifestările clinice cuprind anemie, trombocitopenie, hepatosplenomegalie, limfadenopatie și sindrom de hipervâscozitate. Raportăm cazul unui pacient de 42 de ani, care s-a prezentat pentru scădere ponderală involuntară. Diagnosticul de MW a fost stabilit în baza examinărilor morfologice și imunohistochimice ale măduvei osoase, coroborate cu nivele serice crescute ale IgM. S-a inițiat chimioterapie cu ciclofosfamidă, bortezomib, dexametazonă, la care s-a adăugat, 4 luni mai tâziu, rituximab. După 5 luni de tratament, pacientul a prezentat recădere hematologică, sindrom de hipervâscozitate și insuficiență renală acută. Ecocardiografia a relevat dilatarea ventriculului drept, cu scăderea funcției sistolice globale și hipertensiune pulmonară severă, cu prezervarea volumelor și a funcției sistolice a ventriculului stâng. În ciuda tratamentului medicamentos maximal, pacientul a decedat în ziua a șasea de spitalizare. Particularitatea cazului este reprezentată de evoluția galopantă a unei neoplazii hematologice rare, la un pacient tânăr, fără factori de risc sau istoric cardiovascular, care a manifestat cardiotoxicitate tardivă cu afectare izolată de ventricul drept, în pofida schemei chimioterapice maxime și a abordării multidisciplinare.

Cuvinte cheie

Macroglobulinemia Waldenström, sindrom de hipervâscozitate, insuficiență cardiac dreaptă, hipertensiune pulmonară, cardiotoxicitate.

Abbreviations

2D = 2-dimensional

3D = 3-dimensional

CyBorD = cyclophosphamide, bortezomib, dexamethasone

ECG = electrocardiography

EF = ejection fraction

FAC = fractional area change

GLS = global longitudinal strain

hsTp = high sensitive troponin

IgM = immunoglobulines M

LS = longitudinal strain

LV = left ventricular

LVEF = left ventricular ejection fraction

MRI = magnetic resonance imaging

NT-pro-BNP = N-terminal brain natriuretic peptide

RV = right ventricle

RVEF = right ventricular ejection fraction

sPAP = systolic pulmonary artery pressure

TAPSE = tricuspid annulus systolic excursion

WM = Waldenström macroglobulinemia

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Introduction

Waldenström macroglobulinemia (WM) is a low-grade B-cell clonal disorder characterized by lymphoplasmacytic bone marrow involvement related to monoclonal immunoglobulin M (IgM) that typically results in a poor prognosis [1]. IgM paraprotein systemic deposits can cause various symptoms compatible with systemic amyloidosis, cryoglobulinemia or peripheral neuropathy [2]. Clinical features include anemia, thrombocytopenia, hepatosplenomegaly, lymphadenopathy and hyperviscosity [3]. When IgM protein level is above 30- 40g/L, hyperviscosity syndrome favors the occurrence of pulmonary hypertension, congestive heart failure and cardiovascular collapse [1-3].

Case report

We present the case of a 42-year-old normal weight (body mass index = 25,45 kg/m²) male, admitted in the Hematology Department of our hospital with extreme fatigue, dizziness, vertigo, unexplained weight loss of 10 kilograms in one month and multiple ecchymosis. Based on the hematological evaluation, the patient was diagnosed with WM. He started CyBORd chemotherapy regimen (cyclophosphamide 300mg/m², bortezomib 1.3mg/m², dexamethasone 40mg).

Prior to cytotoxic treatment, the patient underwent baseline cardiac evaluation with clinical examination, electrocardiography (ECG), cardiac biomarkers of myocardial injury (high sensitive troponin -hsTp) and high preload (N-terminal brain natriuretic peptide - NT-pro-BNP) and echocardiography. At baseline, the patient was asymptomatic with no signs or symptoms of heart failure. Initial cardiac biomarkers were within normal range and the ECG did not show any pathological changes. Echocardiographic assessment indicated normal 3-dimensional (3D) left ventricular (LV) volumes and ejection fraction (EF) of 67%, with normal 2-dimensional (2D) global longitudinal strain (GLS) of -21%. Right ventricle (RV) had also normal volumes and function, with tricuspid annulus systolic excursion (TAPSE) of 24mm, fractional area change (FAC) of 42%, free wall LS of -25% and 3D EF of 57% (Figure 1). After the first cycle of chemotherapy, echocardiographic parameters remained unchanged.

Afterwards, the patient's option was to continue chemotherapy in his hometown, where rituximab was added to initial therapy after four months. Five months later, the patient presented to the emergency room of our hospital with dyspnea and marked asthenia, Raynaud syndrome, paresthesia and cyanosis. The clinical examination revealed low blood pressure and sinus tachycardia. Laboratory tests showed increased cardiac biomarkers: hsTp 100ng/ml and NT-pro-BNP 1450pg/ml. Moreover, ECG showed signs of right ventricular overload with positive S₁Q₃T₃ sign and negative T waves in V₁- V₄ leads. Focus echocardiography examination detected dilated right cardiac chambers, reduced TAPSE, pulmonary hypertension, with an estimated value of 83 mmHg for systolic pulmonary artery pressure (sPAP), mild pericardial effusion and preserved 2D LVEF. Corroborating the thromboembolic risk of the hematological

condition, and the clinical presentation with right ventricular overload signs, acute pulmonary embolism was the presumptive diagnosis. Thoracic computed tomography revealed an optimal opacification of pulmonary arteries without thrombi, dilated right heart chambers, mild pleural effusion and no pulmonary parenchymal pathology (Figure 2). Furthermore, the patient was admitted in the hematology department with relapse of the hematological disease and severe hyperviscosity syndrome with a viscosity index of 10 cp. The patient underwent emergency plasmapheresis and the level of viscosity index decreased to 3.2cp. In accordance with the current heart failure guideline recommendations [4], treatment with loop and anti-aldosterone diuretic, and non-dihydropyridine calcium channel blockers, was started. Angiotensin-converting enzyme inhibitors could not be administrated due to reduced blood pressure. Despite optimized cardiovascular therapy, echocardiographic assessment diagnosed persistent pulmonary hypertension, dilated RV with reduced functional parameters: TAPSE= 15mm, 2D LS = -14%, FAC = 26%, and 3D RVEF = 35% (Figure 3).

In order to provide additional information on the possible pathophysiological mechanism of cardiac injury, a cardiac magnetic resonance imaging (MRI) was performed. MRI confirmed right heart dysfunction, with a RVEF of 31%, but there was no evidence of edema or lipomatous changes on T1 and T2 sequences. Moreover, late gadolinium enhancement was confined only to the septal insertion of right ventricular free wall (Figure 4). Unfortunately, despite maximal medical therapy and a specific multidisciplinary approach, the patient's outcome was negative, with his death on day six of hospitalization.

Discussion

Symptomatic hyperviscosity syndrome with secondary pulmonary hypertension may occur in 10-30% of WM patients because of an increased level of immunoglobulin IgM, which results in high morbidity and mortality [5]. In addition, Consuegra et al. have suggested that another mechanism for pulmonary hypertension in WM is represented by diffuse interstitial lung disease, as the first manifestation of the hematological disease [6]. In our case, we excluded the pulmonary disease by thoracic computer tomography, but hyperviscosity index at admission was high. Moreover, hyperviscosity syndrome is a life-threatening condition that occurs not only in malignant diseases but also in autoimmune disorders such as rheumatoid arthritis and Sjogren's disease [7,8]. Two possible mechanisms are suggested: aggregation of immunoglobulins M or G and high level of circulating immune complexes [7].

Clinically, hyperviscosity syndrome includes visual abnormalities, neurological symptoms, such as headache and dizziness, renal dysfunction, pulmonary hypertension and cardiac failure [5]. If data about hyperviscosity and its ocular, neurological and renal consequences is reported [9-11], literature concerning physiopathological relation between hyperviscosity syndrome and secondary pulmonary hypertension with subsequent right ventricular heart failure is scarce.

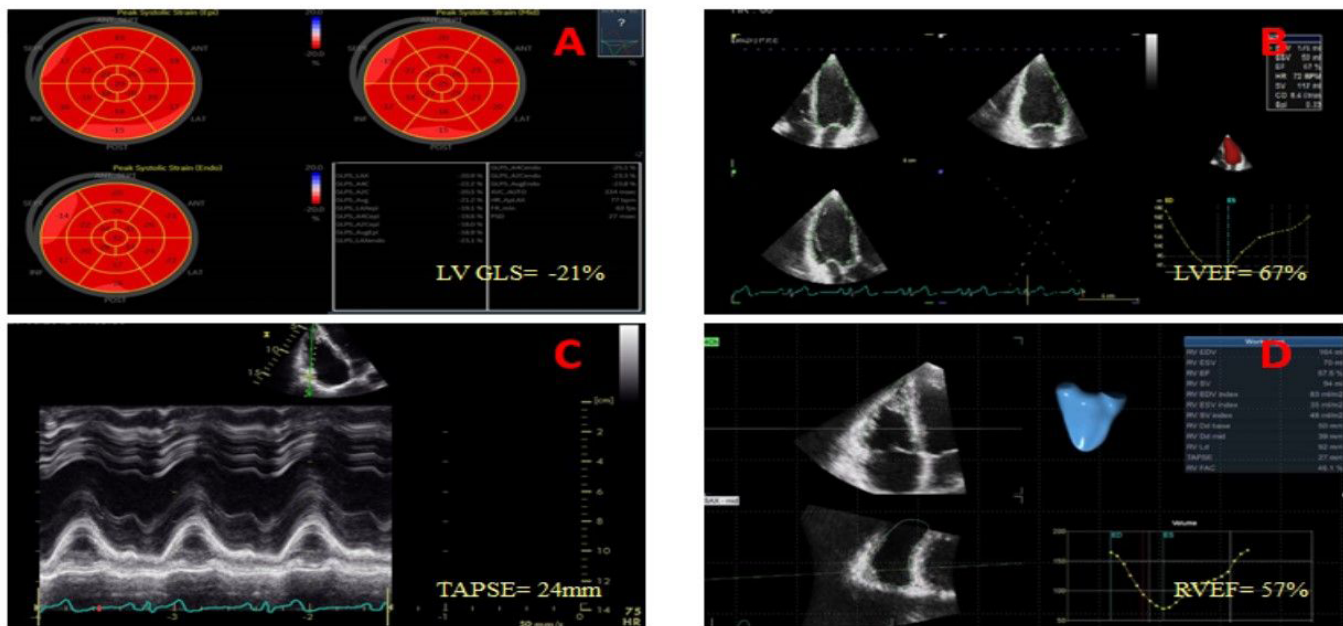


Figure 1 - Baseline echocardiographic evaluation of left ventricular and right ventricular function. Panel A. Normal range left ventricular 2D global longitudinal strain value; Panel B. 3D echocardiographic quantification of left ventricular volumes and ejection fraction showed values within normal limits; Panel C. M-mode analysis with normal tricuspid annulus systolic excursion; Panel D. 3D echocardiographic assessment of the right ventricle revealed also normal volumes and function.

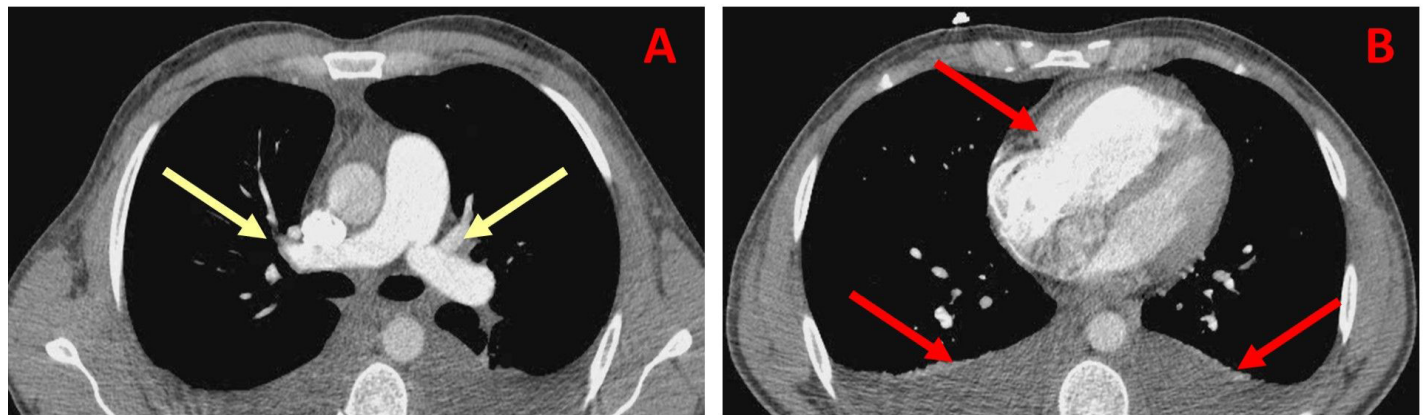


Figure 2 - Thoracic computed tomography. Panel A. Thoracic CT scan with contrast revealed an optimal opacification of pulmonary arteries, without thrombi; Panel B. Dilated right heart chambers, mild pleural effusion and no pulmonary parenchymal pathology.

However, in our case, another mechanism for right heart failure, in addition to hyperviscosity syndrome, may be represented by late chemotherapy-related cardiotoxicity. CyBORd regimen (cyclophosphamide, bortezomib, dexamethasone), in addition to rituximab, is very efficient in achieving complete remission of WM but has various side effects [3]. Cardiotoxicity is the most feared adverse reaction of oncological therapy that causes increased morbidity and mortality in cancer survivors [12]. Myocardial dysfunction secondary to chemotherapy may lead to irreversible cardiomyopathy and heart failure [13]. Echocardiography is the method of choice for monitoring oncological patients before, during and after chemotherapy because it is noninvasive, available, cost-effective and highly reproducible

[14,15]. Cardiotoxicity is defined as LVEF decrease below 50%, with more than 10 percentage points, evaluated 2-3 weeks after initiation of chemotherapy [15]. No standardized definition for chemotherapy-related RV dysfunction is available in current guidelines.

Pulmonary hypertension and right heart failure are rare but severe side effects of chemotherapy or stem cell bone marrow transplantation [15]. Cyclophosphamide, tyrosine kinase inhibitors, such as dasatinib and proteasome inhibitors, such as bortezomib and carfilzomib favor late precapillary pulmonary hypertension after 8-40 months from the first exposure [15,16].

Cardiotoxicity due to cyclophosphamide is rare, in less than 2% of cases and is manifested by arrhythmias, thromboembolic

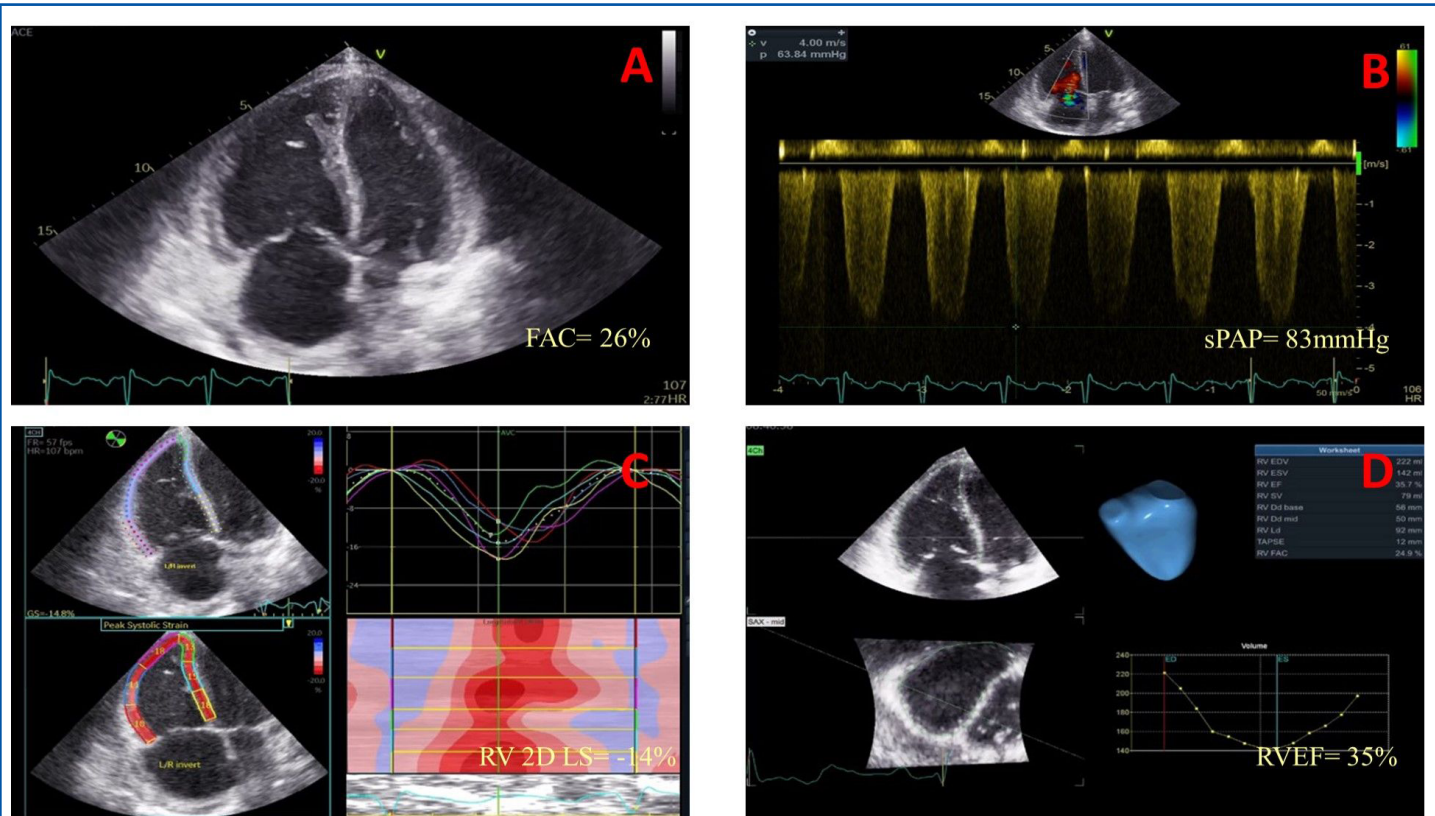


Figure 3 - Echocardiographic assessment after five months when the patient presented relapse of the hematological disease with severe hyperviscosity syndrome revealed impaired right ventricular function. Panel A. Decreased fractional area change value; Panel B. CW interrogation of tricuspid regurgitant jet indicated maximum gradient of 63mmHg, with estimated systolic pulmonary artery pressure of 83mmHg suggesting severe pulmonary hypertension; Panel C. Reduced 2D right ventricular free wall longitudinal strain; Panel D: 3D echocardiographic quantification with reduced right ventricular ejection fraction.

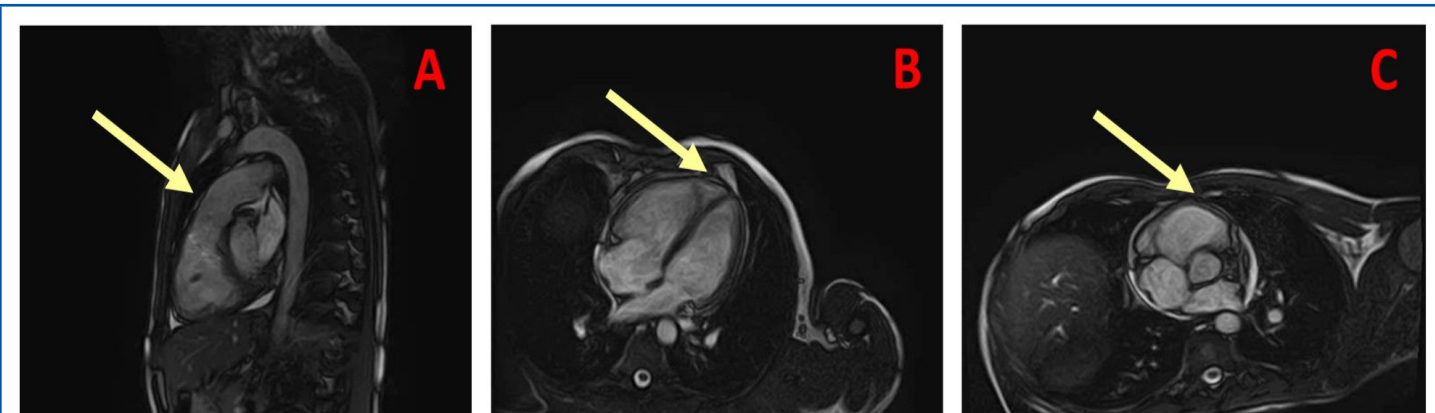


Figure 4 - Cardiac magnetic resonance imaging was performed in order to provide additional information on the possible pathophysiological mechanism of cardiac injury. Panel A. MRI confirmed right heart dysfunction, with a RVEF of 31%; Panel B and C. There was no evidence of edema or lipomatous changes on T1 and T2 sequences. Late gadolinium enhancement was confined only to the septal insertion of right ventricular free wall.

disease and pericardial or pleural effusion [13,16]. Moreover, cyclophosphamide may induce congestive heart failure, with biventricular systolic dysfunction; histopathological exam reveals myocardial hemorrhage and yellowish pericardial effusion [17,18]. Our patient did not experience any arrhythmia or thromboembolic event, only right heart failure; in addition, left ventricular function

remained preserved. Bortezomib related- cardiotoxicity includes arrhythmias, atrioventricular conduction disorders, coronary artery disease, orthostatic hypotension, pericardial effusion and congestive heart failure [16]. Dexamethasone is a potent adjuvant drug to chemotherapy, with anti-inflammatory and immunosuppressive effects. This corticosteroid may lead to cardiac remodeling

and diastolic dysfunction [19]. Cardiovascular toxicity due to rituximab occurs in 8% of the patients; it includes ventricular and supraventricular tachycardia, coronary vasospasm, Takotsubo cardiomyopathy but also arterial pulmonary hypertension with right heart failure and preserved systolic LV function [20-22].

Our case is distinguished by the isolated right ventricular dysfunction and pulmonary hypertension due to the intricate physiopathological pathways involved, including hyperviscosity syndrome and chemotherapy-related cardiotoxicity. Fulminant evolution of the disease did not permit thorough investigation and cardiovascular mechanism involvement confirmation.

Conclusion

Waldenström macroglobulinemia is a rare hematological disease, and literature concerning its cardiovascular complications is lacking. Our case is represented in particular by the rapidly evolving rare haematological condition despite targeted combined cytotoxic regimen and multidisciplinary (cardiologist, haemathologist, radiologist) monitoring combined with a possible late chemotherapy-induced cardiotoxicity. These two mechanisms determined arterial pulmonary hypertension and right heart failure, with preserved left ventricular function with a poor prognosis and the patient's death

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despite maximal medical therapy. On the one hand, further studies are warranted to improve Waldenström macroglobulinemia diagnosis and timely intervention for prompt detection of the wide spectrum of complications and on the other hand for better monitoring of myocardial function during chemotherapy and early intervention.

Conflict of interest

The authors declare no competing interests.

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