Case series, chemotherapy-induced cardiomyopathy: mind the family history!

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Background	Cardiotoxicity presenting as cardiomyopathy is a common side effect in cancer treatment especially with anthracyclines. The role of genetic predisposition is still being investigated.
Case summary	Four unrelated patients with a familial burden for cardiac disease, who developed cardiomyopathy after anthracycline treatment are presented. Case 1 received chemotherapy for breast cancer and developed a dilated left ventricle just after treatment. Her father had died unexpectedly while being screened for heart transplant. Case 2 was known with a family history of sudden cardiac death prior to her breast cancer diagnosis. She received anthracycline-containing chemotherapy treatment twice in 5 years due to recurrence of breast cancer. During that period, two brothers developed a cardiomyopathy. Eighteen years later, a genetic predisposition for cardiomyopathy was ascertained and at screening an asymptomatic non-ischaemic cardiomyopathy was established. Case 3 was diagnosed with a dilated cardiomyopathy 1 year after chemotherapy treatment for breast cancer. Her mother had developed a dilated cardiomyopathy several years before. Case 4 received chemotherapy treatment for Non-Hodgkin's lymphoma and developed dilated cardiomyopathy 1 year later. His brother died from congestive heart failure which he developed after chemotherapy for Non-Hodgkin's lymphoma and a grandmother had died suddenly during child delivery. In all four cases, genetic screening showed (likely) pathogenic variants in cardiomyopathy-associated genes.
Discussion	Current guidelines recommend cardiac evaluation in cancer patients receiving chemotherapy based on the presence of cardiovascular risk factors at the start of treatment. This series emphasizes the importance of including a thorough family history in this process.
Keywords	Cardiomyopathies/chemically induced • Cardiomyopathies/genetics • Genetic predisposition to disease • Anthracyclines • Case series

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Learning points

- Patients with genetic predisposition or family history for cardiomyopathy are at higher risk for chemotherapy-induced cardiomyopathy.
- A genetic predisposition for the development of chemotherapy-induced cardiomyopathy has so far been described for (likely) pathogenic variants in genes such as *MYH7* and *TTN*. A combination of such genes may also be involved.
- Our recommendation for current practice is that family history regarding cardiomyopathy and sudden death should be carefully evaluated in cancer patients prior to starting chemotherapy and genetic testing should be considered accordingly.

Introduction

One of the major complications associated with anticancer treatment is cardiotoxicity.[1] Cardiotoxicity has been described for various treatment modalities but is a prime issue following anthracycline treatment.[2,3] Anthracyclines are currently widely used and have a high efficacy in the treatment of solid tumours (e.g. breast cancer) and haematological malignancies.[4,5] Cardiotoxicity presenting as heart failure in chemotherapy-induced cardiomyopathy (CCM) is described in approximately 5% of patients treated with anthracyclines and is dose related.[3,6,7] In the current era, with the improvement of anticancer treatment, cardiotoxicity causes a significant increase in morbidity and mortality in survivors of cancer.[1] The importance of identifying cancer patients who are at risk for cardiotoxicity has been acknowledged both by the European Society of Cardiology (ESC)[8] as well as the European Society for Medical Oncology (ESMO).[9]

Risk factors that have been identified in numerous studies related to pre-existing cardiovascular disease (e.g. myocardial ischaemia), cardiovascular risk factors such as hypertension and diabetes, previous and planned cardiotoxic cancer treatment including cumulative dose of anthracyclines, and lifestyle and demographic risk factors.[8] Less clear is the evidence on genetic susceptibility or predisposition for developing cardiotoxicity after treatment with chemotherapeutic agents. For many diseases, the personal single nucleotide polymorphism profile partly defines someone's risk for a specific disease. Susceptibility of SNPs regarding the transport, the metabolism, the cytotoxic effect, and the apoptotic sensitivity of chemotherapeutic agents have been found but results are inconsistent.[10] Regarding the role of rare oncogenetic variants, associations between a genetic predisposition for breast cancer (based on pathogenic variants in *BRCA1* (OMIM * 113705) and *BRCA2* (OMIM * 600185) genes) and CCM has been suggested, even though the studies performed to date have not shown consistent findings.[11,12] Furthermore, Young *et al.*[13] suggested a possible genetic predisposition for enhanced susceptibility to anthracyclines while describing a sibling who both developed anthracycline cardiotoxicity following treatment of early breast cancer. Moreover, several case reports[14–16] and two studies[17,18] have described (likely) pathogenic variants in cardiomyopathy genes (*TTN* (OMIM *188840) and *MYH7* (OMIM * 160760) in particular) in chemotherapy-treated patients developing CCM, suggesting that a genetic predisposition for cardiomyopathy might also be a baseline risk factor.

In this case series, four unrelated patients with CCM who received chemotherapy without prior cardiac evaluation or follow-up in spite of a family history for cardiomyopathy and/or sudden death are reported. These findings emphasize the importance of including the cardiovascular family history in the baseline risk factors for cardiotoxicity.

Timeline

Case 1

2003	Father sudden cardiac death at 56 years and known cardiomyopathy.
April 2014	Breast cancer treated with mastectomy and adjuvant chemotherapy with four cycles of doxorubicin (cumulative dose 222 mg/m^2) and cyclophosphamide, 12 times weekly paclitaxel followed by tamoxifen.
December 2014	*BRCA2* pathogenic variant identified NM_000059.3, c.1813dupA, p.(Ile605Asn*fs**11)
January 2015	Palpitations and dizziness. Dilated left ventricle (LV) with reduced LV ejection fraction (LVEF 40%). Treated with heart failure medication including enalapril (5 mg once a day) and carvedilol (3.125 mg twice a day) titrated up to maximum tolerated dosage.
July 2015	Improved LVEF (50%).
March 2018	Reduced exercise capacity. Deterioration of LVEF (28%). Treated with eplerenone (25 mg 3 days per week) in addition to enalapril (10 mg two times a day) and carvedilol (12.5 mg two times a day).
June 2018	*TTN* likely pathogenic variant identified, paternally inherited. NM_133378.4, c.63850dup, p.(Ser21284Phe*fs**2)

Case 2

<1995	Father died suddenly at age 69 years. Six of his 12 sibs died unexpectedly at ages 58–81 years. Older brother had an out-of-hospital cardiac arrest (age 52 years) in the setting of myocardial infarction.
1995	Breast cancer treated with radical mastectomy, radiotherapy, and six cycles of cyclophosphamide, methotrexate, and fluorouracil as adjuvant treatment.
2000/2001	Contralateral breast cancer treated with a breast-conserving surgery, 2 months of radiotherapy, four cycles of doxorubicin/cyclophosphamide (cumulative dose anthracycline 240 mg/m^2), and 5 years tamoxifen 20 mg daily.

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Case 2	
	Younger brother with dilated cardiomyopathy (DCM) and frequent ventricular arrhythmias. Implantable cardioverter-defibrillator (ICD) implantation.
2011	Palpitations. Echocardiogram: reduced LVEF (40%). Coronary angiogram: no obstructive disease. Heart failure medication was started including perindopril (2 mg once a day) and nebivolol (1.25 mg once a day).
2015	Younger brother undergoes heart transplant and *TTN* likely pathogenic variant identified.
2019	Reduced LVEF (45%). Carrier *TTN* likely pathogenic variant. NM_133378.4, c.46214del, p.(Gly15405Glu*fs**18)
Case 3	
2001	Mother dilated cardiomyopathy and ICD implantation.
October 2017	Breast cancer treated with four cycles of doxorubicin/cyclophosphamide (cumulative dose anthracycline 240 mg/m^2) and four cycles of docetaxel as neo-adjuvant treatment, followed by local excision and sentinel node and adjuvant radiotherapy.
June 2018	Extreme fatigue. Dilated LV with poor LVEF fraction (17%). Heart failure medication was started including doses (perindopril 4 mg once a day, carvedilol 6.25 mg two times a day, eplerenone 25 mg once a day) and ivabradine.
July 2018	ICD implantation.
September 2019	Improved LVEF (48%)
March 2020	*TNNT2* pathogenic variant identified, maternally inherited. NM_001276347.1, c.556G>A, p.(Gly186Ser)
Case 4	
1988	Death of brother (at 32 years) with dilated cardiomyopathy following chemotherapy for Non-Hodgkin lymphoma. Paternal grandmother died at age 36 during child delivery.
2017	Non-Hodgkin lymphoma treated with chemotherapy consisting of 6 cycles of R-CHOP [rituximab, cyclophosphamide, doxorubicin (cumulative dose 300 mg/m^2), vincristine and prednisolone].
March 2019	Dyspnoea. Dilated LV with reduced LVEF (20%). Heart failure medication was initiated including ramipril (2.5 mg two times a day) and bisoprolol (5 mg once a day) and furosemide was started.
May 2019	ICD implantation.
March 2020	*MYH7* pathogenic and *TTN* likely pathogenic variants identified. *MYH7*: NM_000257.2, c.5754C>G, p.(Asn1918Lys) *TTN*: NM_001267550.1, c.45823_45848del, p.(Ala15275ser*fs**4)

Case presentation

Case 1

A 38-year-old woman was diagnosed with ductal carcinoma *in situ* (T2N1M0) in her left breast based on a pathogenic variant in *BRCA2* (c.1813dupA, *p.*(Ile605Asn*fs**11) in exon 10; NM_000059.3). The treatment consisted of a radical mastectomy followed by adjuvant treatment with four cycles of doxorubicin (cumulative dose 222 mg/m^2) and cyclophosphamide, 12 times weekly paclitaxel followed by tamoxifen. After treatment was finished, the patient presented with palpitations and dizziness. She had no medical history and her only cardiovascular risk factor was smoking. Her blood pressure was normal (110/70 mmHg), and the electrocardiogram (ECG) showed no abnormalities but the echocardiography displayed a dilated left ventricle (LV) with a reduced left ventricular ejection fraction (LVEF) of 40%. She was treated with heart failure medication including enalapril (5 mg once a day) and carvedilol (3.125 mg twice a day) titrated up to the maximum tolerated dosage until complaints of orthostatic hypotension occurred. Her LVEF recovered to 50%, where after she was discharged from further follow-up. Three years later, the patient presented with reduced exercise capacity and was referred to our cardiogenetic department. During this presentation, she showed no signs of fluid overload at the physical examination. Her N-terminal pro-b-type natriuretic peptide (NT-proBNP) was increased (2584 ng/L), and Troponin T (TropT) was normal (4 ng/L). Cardiological evaluation showed non-specific repolarization disorders on the ECG and the echocardiography showed a dilated LV with a reduced systolic function (LVEF 28%). Cardiac magnetic resonance imaging (MRI) showed a dilated LV with EF of 26%. Delayed enhancement was only seen at the RV–LV insertion. Heart failure medication was optimized during bi-weekly controls by adding eplerenone (25 mg 3 days per week) in addition to enalapril (10 mg two times a day) and carvedilol (12.5 mg two times a day). Thereafter, echocardiogram showed partial recovery of the LV function to a LVEF of 35% at 1-year follow-up. Family history revealed that her father died suddenly at the age of 56 years while being screened for heart transplant, possibly of a ventricular arrhythmia in the context of a dilated cardiomyopathy (DCM). DNA analysis of 61 genes associated with cardiomyopathy identified a paternally inherited likely pathogenic variant in the *TTN* gene (NM_133378.4(TTN):c.63850dup *p.*(Ser21284Phe*fs**2)).

Case 2

At the age of 51 years, this patient was diagnosed with breast cancer (ductal carcinoma with three positive nodes), for which she underwent a radical mastectomy, radiotherapy, and six cycles of cyclophosphamide, methotrexate, and fluorouracil as adjuvant treatment. Five years later, she was diagnosed with contralateral breast cancer, treated with a breast-conserving surgery, 2 months of radiotherapy, four cycles of doxorubicin/cyclophosphamide (cumulative dose anthracycline 240 mg/m^2), and 5 years tamoxifen 20 mg daily.

At the time of her first treatment, it was known that she had a positive family history for cardiac arrest: her father and 6 of his 12 siblings died suddenly, respectively at ages 69 and between 58- and 81 years. Her older brother had just been resuscitated after an out-of-hospital cardiac arrest in the context of a myocardial infarction at the age of 52 years. By the time she underwent her second chemotherapy

treatment, her younger brother had developed a DCM at the age of 49 years. He received an implantable cardioverter-defibrillator (ICD) because he had frequent ventricular arrhythmias. Genetic testing of four genes (*MYBPC3*, *MYH7*, *TNNT2*, *LMNA*) in his brother revealed no pathogenic variants. Genetic re-analysis using a broader panel of 47 genes 14 years later, at the time he underwent a heart transplant, showed a likely pathogenic variant in the *TTN* gene (c.46214del; p.(Gly15405Glu*fs**18); NM_133378.4).

She was referred to the cardiologist at the age of 67 years because she had palpitations. She showed no signs of fluid overload at the physical examination. An echocardiogram showed a reduced LVEF of 40% and heart failure medication was started in low doses of perindopril (2 mg once a day) and nebivolol (1.25 mg once a day). Follow-up visits were scheduled every 2 weeks with the heart failure nurse for up-titration of the medication; however, dizziness limited further increase of the doses. Eight years later, after the genetic predisposition for cardiomyopathy was found in her brother, the patient underwent re-evaluation for cardiac function and genetic testing. Results showed that she was heterozygous for the truncating *TTN* variant identified previously in her brother and that her LV function remained reduced with an LVEF of 45%.

Case 3

At the age of 46 years, this patient presented with extreme fatigue caused by heart failure de novo (NYHA Class III). Physical examination showed jugular vein distension and peripheral oedema of the lower extremities. Echocardiography revealed a dilated LV (LVEF of 17% with overall hypokinesia). She had no significant coronary artery disease. Cardiac MRI showed dilated LV with EF of 18% without delayed enhancement. Heart failure medication was started including perindopril, carvedilol, and furosemide. Follow-up visits were scheduled bi-weekly for up-titration of the medication up to the maximum tolerated doses (perindopril 4 mg once a day, carvedilol 6.25 mg two times a day, eplerenone 25 mg once a day). In addition, ivabradine was started because of heart rate >70 b.p.m. Side effects for this patient were low blood pressure (100/60 mmHg) and dizziness (the four-chamber view at baseline, at 3 months, and at 1-year follow-up is added in the Supplementary material online). Family history revealed that her mother had been diagnosed with heart failure based on DCM for which she had received an ICD. Eight months before her presentation, the patient had been diagnosed with breast cancer (triple-negative cT3N3MO multifocal adenocarcinoma) and was treated with four cycles of doxorubicin/cyclophosphamide (cumulative dose anthracycline 240 mg/m^2) and four cycles of docetaxel as neo-adjuvant treatment, followed by local excision and sentinel node and adjuvant radiotherapy because of cardiomyopathy. Genetic diagnostics was performed because of suspected familial cardiomyopathy. Based on a panel of 61 genes related to cardiomyopathy, a maternally inherited pathogenic variant was found in the *TNNT2* gene (OMIM * 191045)(c.556G>A p.(Gly186Ser) [NM_001276347.1]). This variant is classified as pathogenic based on haplotype analysis in four unrelated families.

Case 4

A 57-year-old male was diagnosed with a diffuse large B-cell non-Hodgkin's lymphoma stage 3 for which he was treated with

chemotherapy consisting of six cycles of R-CHOP [rituximab, cyclophosphamide, doxorubicin (cumulative dose 300 mg/m^2), vincristine, and prednisolone]. Complete remission was attained 6 months later. A year thereafter, the patient presented with near syncope. He showed no signs of fluid overload at the physical examination. His NT-proBNP was significantly increased (8439 ng/L) and his Trop T was slightly increased as well (26 ng/L). Dilated cardiomyopathy was diagnosed with an LVEF of 20% and non-sustained ventricular tachycardias were recorded on Holter monitoring. Furosemide was started and heart failure medication was initiated including ramipril (2.5 mg two times a day) and bisoprolol (5 mg once a day) with bi-weekly follow-up visits for up-titration to the maximum tolerated dosage and an ICD was implanted.

His brother was diagnosed with non-Hodgkin lymphoma at the age of 23 years and was treated with chemotherapy. Three years later, recurrence of the lymphoma occurred and cytostatic treatment was again initiated leading to remission (cumulative dose anthracycline 630 mg/m^2). Six years thereafter, he developed symptoms of dyspnoea and was diagnosed with DCM most likely cardiotoxic due to a high dose of doxorubicin. He died at the age of 32 years of an acute pulmonary embolism while awaiting a heart transplant. Family history also showed a paternal grandmother who died suddenly at the age of 36 years during delivery.

Genetic testing of a cardiomyopathy panel containing 62 genes in our patient revealed a pathogenic variant in the *MYH7* gene (c.5754C>G, p.(Asn1918Lys); NM_000257.2,[19] and a likely pathogenic variant in the *TTN* gene (c.45823_45848del, p.(Ala15275ser*fs**4); NM_001267550.1). A genealogical study showed that his paternal grandmother (as well as his father who died at the age of 66 years following lung cancer) was an obligate carrier of the *MYH7* pathogenic variant. The DNA test on the paraffin material of his father and brother was inconclusive due to the low quality of the isolated DNA.

Discussion

In this case series, four unrelated patients with CCM who received chemotherapy without prior cardiac evaluation or follow-up in spite of a family history for cardiomyopathy and/or sudden death are reported. Despite the family history, the cardiomyopathy was established after cardiac complaints occurred. More attention to the family history and genetic background of these patients could have led to an earlier and better treatment of the cardiomyopathy and/or prevented the cardiac problems.

Previous case reports have suggested that a genetic predisposition for cardiomyopathy (in genes such as *MYH7* and *TTN*) may contribute to the individual susceptibility for developing CCM.[14–16] The current case series adds more cases to the literature and shows that a combination of such genes (such as *MYH7 and TTN* in Case 4) can also be involved in the individual susceptibility for developing CCM. This latter finding raises the question whether double pathogenic variants in these genes increase the likelihood of developing CCM. It is, in this context, unfortunate that DNA testing on paraffin material of the deceased brother in Case 4 was not feasible. Likewise, a combination of both genetic predisposition for breast cancer as well as for cardiomyopathy (*BRCA2 and TTN* in Case 1) may lead to a higher risk of developing CCM. Clear evidence for a causal role of cardiomyopathy

genes (as well as *BRCA* genes—but this is beyond the scope of this article) in the development of CCM is still lacking. In addition to previous case reports, Wasielewski *et al.*[17] identified two families with pathogenic variants in the *MYH7* gene by testing 21 CCM patients from CCM/DCM families based on different hospital-based registries. Garcia-Pavia *et al.*[18] compared the frequency of rare variants in cardiomyopathy-related genes between patients treated with anthracyclines and healthy controls and found a significant increase in *TTN* truncating variants in the cohort group. All the patients described in this case series had received lower doses of anthracycline chemotherapy, doxorubicin, than the maximum cumulative doses allowed (between $220\,mg/m^2$ in Case 1 and $300\,mg/m^2$ in Case 4) than is maximally allowed ($550\,mg/m^2$).[20] As such, CCM can be seen as an initial manifestation of familial DCM in the context of a *TTN* genetic predisposition in the same way as peripartum cardiomyopathy (PPCM) has been described to be part of familial DCM.[21,22] Moreover, CCM and PPCM are found to be quite comparable as both are the result of a complex balance between cardiomyocyte and endothelial homeostasis on the basis of a number of mechanisms such as reactive oxidative stress, interference in apoptosis, growth, and metabolism and angiogenic imbalance.[23]

Recently, the ESC and ESMO have published consensus recommendations on the management of cardiac disease in cancer patients throughout oncological treatment, thereby providing guidance regarding prevention, screening, monitoring, and treatment of cardiovascular toxicity.[8,9] The implementation of cardio-oncology services in various hospitals throughout Europe is currently ongoing,[24] offering numerous possibilities for studying the relationship between baseline risk factors and CCM in a prospective way.

As recommended in the ESMO guidelines and the ESC position statement, our case report confirms the need for a prior imaging before starting anticancer treatment.[9,25] Cardiac MRI imaging and 3D echocardiography are the preferred techniques but limitations such as unavailability, cost, and expertise might have led to a delay in the adoption of these technics. 2D echocardiography using Simpson's biplane method is the method of choice when 3D echocardiography and CMR are not available.[26] The most relevant parameters for initial echocardiography assessment include left ventricular size and left ventricular function. Increased left ventricular size reflects remodelling and fluid status and may identify patients at increased risk for cardiotoxicity. A decrease in left ventricular ejection fraction to less than 40–50% at baseline suggests the need of the initiation of cardioprotective medication before starting treatment. In addition assessment of right ventricular function, pulmonary artery pressure and volume status can be relevant. Before starting chemotherapy including anthracyclines, cardiotoxicity risk can be classified into low/medium/high according to therapy- and patient-related factors.[25] According to this risk classification, echocardiography surveillance intensity can be personalized during the therapy.[25] Similar to anthracycline chemotherapy, in patients on HER2-targeted therapies, standard surveillance including a baseline echocardiogram is indicated and frequency of surveillance can be personalized according to baseline risk assessment of cardiotoxicity.[25] In immune-checkpoint inhibitors cardiomyopathy is not common, however a rare presentation of cardiotoxicity is myocarditis which has been associated with a high mortality rate.[27] Pre-existing heart disease imposes an increased risk for the development

of myocarditis induced by immune-checkpoint inhibitors.[25] In addition, a recent study suggested that subtle reduction in left ventricular function may be an early sign of immune-checkpoint inhibitor-induced myocarditis.[28] Therefore, also in this group a baseline echocardiography could be useful to identify patients at increased risk and to evaluate changes during treatment. Finally, an increased risk of cardiomyopathy during treatment is described in patients treated with the combination of radiotherapy and anthracycline-containing chemotherapy, and in this group, a baseline echocardiogram is suggested.[25]

Although early-onset cardiovascular family history is described as a baseline risk factor in the ESC recommendation for the development of cardiotoxicity, this has so far not been endorsed in the ESMO recommendation.[9]

Based on the current case series, before starting chemotherapy especially with anthracyclines, family history regarding cardiomyopathy or sudden death should be carefully evaluated. Genetic testing and treatment with alternative chemotherapy with less cardiotoxicity should be strongly considered if the patient's family history is positive. In addition, patients with a positive family history should be monitored intensively for the development of cardiotoxicity during and after anticancer treatment.

Lead author biography

Dr. Moghadasi graduated in Medicine and Master of Science in Biomedical Sciences in 2011 and in Master of Epidemiology in 2014. In 2017, she defended her PhD thesis entitled: 'Hereditary breast cancer and the clinical significance of variants in the BRCA1 and BRCA2 genes'. She currently works as a Clinical Geneticist and post-doctoral researcher.

Supplementary material

Supplementary material is available at *European Heart Journal—Case Reports* online.

Slide sets: A fully edited slide set detailing these cases and suitable for local presentation is available online as Supplementary data.

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Consent

The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

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