YOUNG MAN WITH HODGKIN'S LYMPHOMA TREATY WITH CHEMOTHERAPY AND SUDDEN CLINICAL PICTURE OF ACUTE HEART FAILURE

HOMBRE JOVEM COM LINFOMA HODKING TRATADO COM QUIMIOTERAPIA E SÚBITO QUADRO DE FALENCIA CARDIACA AGUDA

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Case report: Jhonatan Franco MD residente de 2 año de medicina interna en el hospital bellvitge de Barcelona, España. Actualmente en rotación por la cardiologia.

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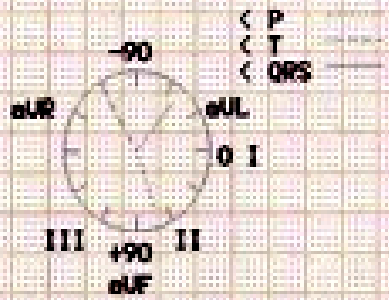
-32-year-old man of Spanish origin, no recent trips.
-Pathological history: stage III Hodgkin's lymphoma, in treatment with CHOP chemotherapy (6 cycles, the last one 4 months ago, according to the last control free of disease, but even so, he undergoes cycles every 2 months with rituximab by new protocol for lymphoma)
-Cardiological history: he says none, no family history.
-Toxicology history: no alcohol, smoking or psychoactive substances. None in relatives.
-Current disease: non-specific and atypical symptoms: 3 days of dry cough, feeling of dyspnea, and non-irradiated oppressive epigastric pain of 4/10 intensity; feeling of palpitations. No autonomic signs.
-Physical examination: BP 100/60, HR 70 bpm, T, 36.5ºC, no jugular ingurgitation or hepatojugular reflux; regular cardiac rhythmic normal sounds, with no murmurs, respiratory sounds with proper ventilation, no rales or hypophonesis, no abdominal hepatomegalia or external symmetrical adenopathies; no edema, bilateral pedal pulses present.
-When he first came to the hospital, an ECG was made So, in spite of such a normal physical examination, it was decided to preformed lab. which showed normal renal function, normal ions, no alteration in transaminases, positive troponins (6 ng/L, reference value 0.2)
-**Emergency echocardiogram**: severe basal septal and anterior hypokinesis with LEVF 40% (no abnormal findings in the rest)
-Cardiac catheterization: healthy coronary arteries with ventriculography that showed LVEF 35%.
-**Diagnostic Hypotesis:** acute myocarditis After 24 hs of being admitted into the coronary unit, ECG 1. He suddenly suffers hemodynamic deterioration with hypotension, respiratory insufficiency (acute pulmonary edema) that requires endotracheal intubation plus use of inotropic and vasoactive drugs, without reaching a complete recovery, so ventricular assist devices are implanted.Presently, we have an endomyocardial biopsy, and the echocardiogram of control shows severe left ventricular hypokinesis and interventricular septum with right ventricular normal contractility. No wall thickening, normal valves

- Hombre de 32 años español, sin viajes recientes.
-Antecedentes patológicos**:** Linfoma de Hodking estadio III en tratamiento con quimioterapia CHOP (6 ciclos el último hace 4 meses. Segun el ultimo control libre de enfermedad pero aun asi, hace ciclos cada 2 meses con rituximab con nuevo protocolo de linfoma).
-Cardiologico antecedentes familiares negativos, Toxicos: no alcohol, tabaco ni sustancias psicoactivas.
- Enfermedad actual: Cuadro inespecifico y atipico: tres dias de tos seca, disnea, dolor epigástrico opresivo no irradiado de intensidad 4/10, palpitaciones. sin vegetatismo.
-Examen fisico: TA 100/60, FC 70 lpm, Tº 36,5 ºc. c/c no ingurgitacion yugular ni reflujo hepatoyugular c/p ruidos cardiacos ritmicos sin soplos ruidos respiratorios con adecuada ventilación, no estertores ni hipofonesis, **Abdomen:** sin hepatomegalia ni adenopatias.
-**Extremidades:** simétricas no edemas pulsos pedios bilaterales presentes.
A su llegada al hospital se realiza el primer ECG. Por lo cual a pesar del examen fisico normal, se decide realizar examenes laboratoriales que evidencian funcion renal normal, ionograma normal, transaminasas normales y aumento de troponinas (6 ng/L. valor de referencia 0,2)
Ecocardiograma de urgencia: hipoquinesia septal basal y anterior con severa disminución de la fracción de eyección 40%
Cateterismo cardiaco: arterias coronarias sanas con ventriculografia que evidenciaba fracción de eyección 35%.Hipótesis diagnostica: miocarditis aguda
A las 24 horas de ingreso sufre subitamente deterioro hemodinamico con hipotension, insuficiencia respiratoria (edema agudo de pulmón) que requiere intubacion endotraqueal y uso de farmacos intrópicos y vasoactivos sin lograr una completa recuperación, por lo cual se implantan dispositivos de asistencia ventricular.
-En el momento estamos esperando el resultado de la biopsia endomiocardica, y el ecocardiograma de control evidencia hipoquinesia severa de vetriculo izquierdo y septo interventricular con vetriculo derecho de contractilidad normal. Paredes de espesor normal y, valvulas normales.

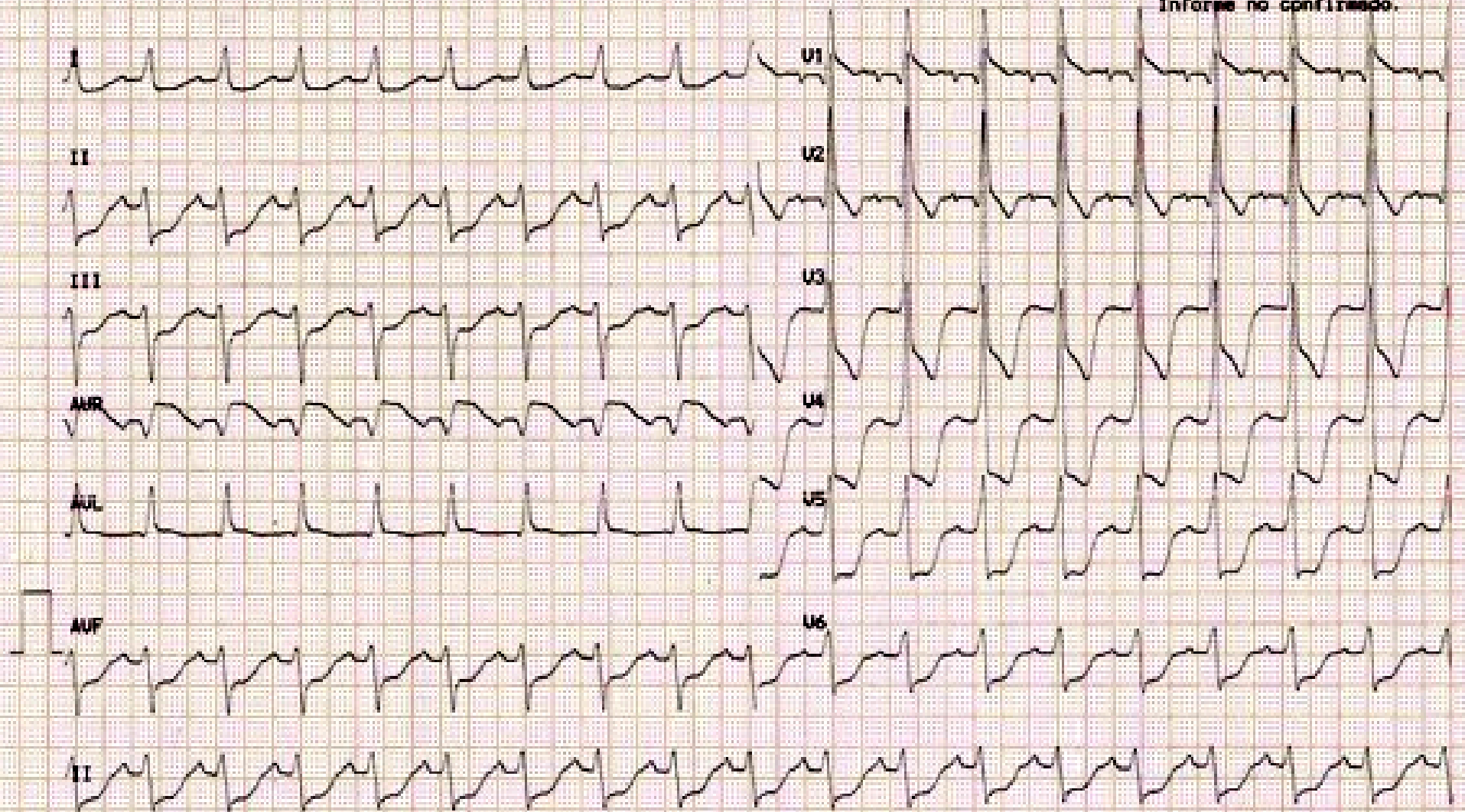
Resultados de medidas:

QRS	:		126 ms
QT/QTcB	:	360 /	484 ms
PQ	:		178 ms
P	:		96 ms
RR/PP	:	548 /	550 ms
P/QRS/T	:	70/ -51/	238 Grad

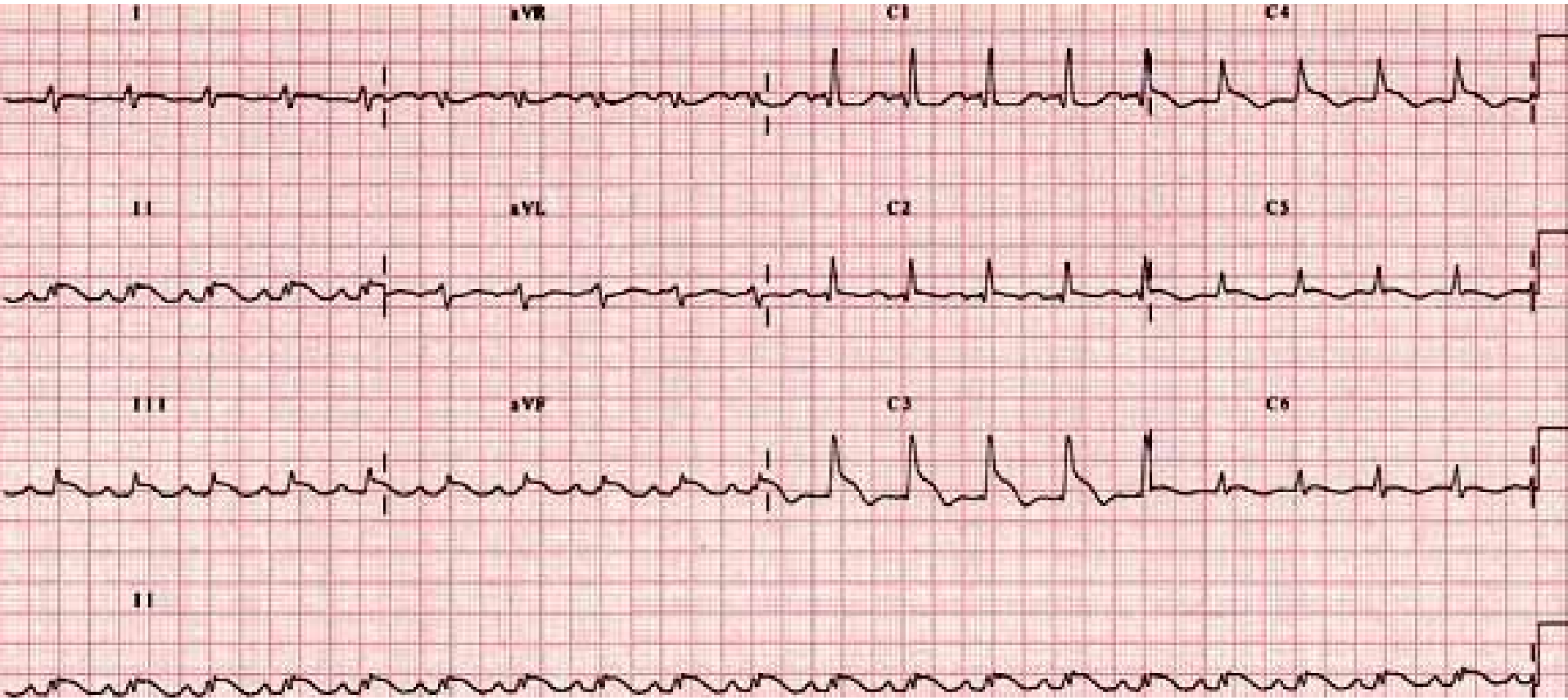


Interpretacion:
TAQUICARDIA SINUSAL
POSIBLE CRECIMIENTO AURICULAR IZQUIERDO
DESVIACION DEL EJE IZQUIERDO
BLOQUEO DE LA RAMA DERECHA
INFARTO SEPTAL , EDAD INDETERMINADA
MARCADA ANORMALIDAD DE LA ONDA T, CONSIDERESE ISQUEMIA INFEROLATERAL
ECG ANORMAL

Informe no confirmado.



6 hours later from first ECG



Dear Andres,

This unfortunate man has suffered severe myocardial damage (cardiomyopathy) secondary to the cardiotoxic effects of his ongoing chemotherapy. Some of the damage is probably related to chemotherapy induced coronary thrombosis resulting in elevated cardiac enzymes and marked ST segment abnormalities on his ECG's.

The first ECG shows acute injury with marked ST elevation in lead aVR and V1 (which has a lambda QRS-ST configuration and multiple other leads with ST segment depression suggesting injury related to left-main coronary occlusion or triple vessel coronary occlusions. The frontal plane QRS axis is around -60 degrees with S in lead III > S in lead II, and R in aVL > R in aVR characteristic of left anterior fascicular block. In the anterior leads there is prominent anterior forces with an pattern suggestive of left septal fascicular block. The initial q-waves in V1-2 and the absence of q-waves in lead I and V6 indicate initial left ventricular activation through the remaining posterior fascicule (similar to a case you shared with us a few weeks ago). Therefore he has bifascicular block of the left bundle branch. The 2nd ECG 6-hrs later has changes quite different from the first ECG which are somewhat problematic for me. Now he has multiple leads with ST segment elevation and very little reciprocal ST segment depression. The prominent anterior forces remain (septal fascicular block, but the frontal plane QRS axis is now around +90 degrees or slightly more the +90. The PR intervals and heart rates look the same on both ECG's. Overall the QRS voltage is much reduced on this ECG suggesting probable pericardial effusion. I think that the multiple leads with ST segment elevation are due to epicardial injury related to pericarditis (although I don't see any PR segment changes). The change in QRS axis might be related to return of conduction in the left anterior fascicle. Unfortunately the outlook is very poor for this man.

I look forward to colleagues' opinions.

Regards,

Frank

Estimando Andres, Este desafortunado joven hombre ha sufrido un severo daño miocárdico (cardiomiopatia) consecuencia del efecto tóxico de la quimioterapia prolongada. Algo del daño miocárdico probablemente esté relacionado a la quimioterapia inductora de trombosis que resultó en elevación de las enzimas cardiacas y de la marcada elevación del segmento ST en sus ECGs

El primer ECG muestra corriente de lesión aguda con significativa elevación del segmento ST en aVR y V1(el cual tiene la morfologia lamda y muchas otras derivaciones con depresión del ST sugestivo de lesión consecuencia de obstrucción de tronco de coronaria izquierda o lesion de tres vasos. El plano frontal muestra un eje en torno de -60º SIII>II, y R de aVL> R de aVR característico de bloqueo anterosuperior de la rama izquierda.

En las derivaciones precordiales se observa fuerzas anteriores prominentes conun patrón sugestivo de bloqueo del fasciculo medio de la rama izquierda: La q inicial de V1-V2 y la ausencia de q en I y V6 indican activación inicial del VI atravéz del fasciículo pósteroinferior. Consecuentemente este paciente tiene un bloqueo bifascicular izquierdo.

El segundo trazado realizado 6n horas despues es bastante diferente del primero el cual es problemático para mi. Ahora ele tiene elevación del ST en múltiples derivaciones y muy pocos cambios recíprocos. Las fuerzas anterioresprominentes permanecen(Bloqueo de la división media de la rama izquierda) pero en el plano frontal el eje eléctrico del QRS se encuentra ahora en +90º o levemente mas a la derecha.

Los intervalos PR y las frecuencias cardiacas parecen las mismas en ambos ECGs.

El voltage del QRS está reducido sugiriendo derrame pericárdico. Pienso que multiples derivaciuones con elevación del ST pueden estar relacionads con pericarditis apesar que no veo ningun cambio en el segmento PR. Las mudanzas del eje del QRS puede sugerir reversión del bloqueo del fasciculo antero-superior izquierdo. Infelizmente el pronóstico de este hombre es muy sombrio. Espero por opiniones de otros colegas Frank

Dear Dr Perez Riera

In the "Homem Jovem" case I do not see J-waves, only terminal QRS distortion. I think the initial ECG is a variant of "tombstone" ST segments. Also there are either negative terminal T waves or large inverted U waves in V3-6, each suggesting ischemia with a poor prognosis. (What happened to the patient??)Also there is striking PR depression in 2,3 and F without enlarged P waves pericarditis???

Best wishes

David H. Spodick MD, FACC, MACP, FCCP, FAHA

Estimado Dr Pérez Riera En este hombre joven no veo ondas J, apenas una distorción terminal del QRS. Pienso que el primer ECG es una variante de segmento ST tipo "tombostone".

También hay ondas T negativas grandes ondas de U invertidas de V3-6, lo que sugiere isquemia de mal pronóstico. (¿Qué pasó con el paciente?) También me llama la atención la depresión del PR en II, III y aVF sin ondas P aumentadas: pericarditis??

Dr. David H. Spodick attended Bard College and was awarded a Doctorate in Science for his work in the field of noninvasive clinical cardiology and physiology. He interned at St. Francis Hospital in Hartford, and completed his residency training at Beth Israel Hospital and New England Medical Center. He also served in the Air Force, which afforded him the opportunity to travel extensively. Travel later became an integral part of his professional career.

Although Dr. Spodick became interested in the emerging subspecialty of cardiology during his residency, his career started when he became David Littmann's first fellow in cardiology in 1956. After participating as a special post-doctoral fellow, sponsored by the National Heart Institute at the West Roxbury Veterans Administration Hospital, he moved to the Lemuel Shattuck Hospital. He then began a 19 year academic career including academic appointments at all three of the Boston medical schools and read all of the Boston Evening Clinic's electrocardiograms for 15 years without remuneration.

David Spodick became Chief of Cardiology at St. Vincent Hospital in 1976, where he joined Chief of Medicine Gilbert Levinson, an established cardiovascular researcher. Dr. Spodick has remained at St. Vincent Hospital, where he is a skilled practitioner and revered educator. Until recently, he also oversaw the Noninvasive Unit. His academic appointment at the University of Massachusetts Medical School has enriched the young careers of countless medical students.

David Spodick's career as a clinician, researcher, educator, and administrator in cardiovascular medicine continues to evolve after 50 years. He has focused on four areas: noninvasive evaluation of the heart, including physical examination; diseases of the atria; diseases of the pericardium; and electrocardiography. His meticulous examination of all available data and his ability to synthesize the information has led him to become a world expert on the latter two of these topics. As such, he has been referred many difficult cases for second, third, and fourth opinions.

His curriculum vitae includes well over 400 articles, as well as numerous books, chapters, and abstracts. He has held many editorial positions and is an esteemed reviewer for many cardiovascular journals. In 1998, he received the Burger Award of the European Society of Noninvasive Cardiovascular Dynamics. In 2003, Dr. Spodick was awarded the Melvin L. Marcus Memorial Award for his distinguished contribution as a gifted teacher in cardiology by the International Academy of Cardiology at the 3rd World Congress of Heart Disease. His cardiovascular fellows have recognized him with teaching awards on an almost yearly basis.

David Spodick continues to be highly productive in the cardiovascular medical community through his work at St. Vincent Hospital, where he is Director Emeritus of the Cardiovascular Medicine Fellowship Program and at the University of Massachusetts Medical School where he is Professor of Medicine Emeritus.

Tratare de analizar el caso del Dr Jonathan Franco: Otra vez tenemos el ejemplo de un caso de una isquemia circunferencial inducida por una taquicardia sinusal , en presencia de una miocardiopatia no coronaria y otra vez se demuestra la falacia de los que intentan de introducir el concepto equivocado de que elevacion del ST-T elevado en V1 y aVR son indice de obstrucción severa de 3 vasos epicardiales o LMCA, y de esta forma perpetuar un error que lleva a grandes errores diagnósticos. Este terrible caso demuestra una patologia del VI con severa fibrosis subendocardica. La taquicardia sinusal eleva `notariamente la presion diastólica final del VI, induciendo una insuficiencia diastólica severa con signos de insuficiencia cardiaca izquierda

Como me he expresado anteriomente, que la elevacion del ST-T en aVR debido a depresion del segmento ST -T en V6, pero ST-T, pero se registramos los potenciales intracavitarios seran similares a AVR como lo demostro en 1932 Frank Wilson , el descubridor de los potenciales unipolares aumentados, y lo mismo se vera en V1 debido a que indica una remodelación de V5 Y es importante persistir con esta concepcion, ya quese sigue publicando en revistas importantes este concepto erróneo , diciendo que no se debe interpretar de una forma diferente un mismo fenomeno electrofisiologoco fisiologico que aparece en casos agudos isquemicos ,no isquemecos y cronicos ,todos indican un aumento subito o cronico de la presion distolica final esto es otro ejemplo como un simple ECG se puede leer los cambios hemodiamicos que ocurren el VI

El segundo electro es una verdadera castástrofe, el corazon se dilato por completo y el aumentó el volumen sistolico y diastolico que disminununuyen los potenciales electrotonicos. Como hay una elevación del ST-T en todas las derivaciones , sugeriendo una lesion no segmentaria del VI y pero la frecuencia cardiaca no disminuye , pero no aparece ST deprimido porque la lesion ya es transmural y el ventriculo casi no se mueve

Un fraternal abrazo

Samuel Sclarovsky

Esta es una patologia toxica por fármacos antimitóticos , con un pronóstico ominoso.

Estimado Jhonatan,El caso que presentaste es precioso y de una gran potencialidad didáctica. Pero tengo algunos comentarios respecto a las formas y al contenido.

REPECTO A LAS FORMAS: La forma de comunicarlo ha estado lleno de "interferencias" que afectaron el análisis y la comprensión del caso. A pesar de haber acertado con mi planteo inicial, a mi me dejó un sabor raro todo este revoltijo de información. A que me refiero? El primer mail que me llegó, presentaba el caso sin AP. Luego me llegaron comentarios en inglés de eminencias internacionales de la cardiología haciendo mención a quimioterapia en curso?! Luego otro mail diciendo que la última serie fue en Octubre 2009?! Todavía no entiendo a que se debieron todos esos problemas de comunicación. En suma: un caso precioso, una comunicación desordenada y contradictoria. Seguramente el próximo caso saldrá mejor.

RESPECTO AL CONTENIDO: En mi opinión, tu paciente está vivo de milagro, o porque no era su hora todavía. No se si alguien en el mundo tiene experiencia en este tipo de pacientes. Seguramente algún centro hay en el mundo que tenga pero lo desconozco.

Me parece que es un caso para especialistas en miocardiopatías, y este es un foro de arritmólogos (o mejor dicho locos por las arritmias y los ECG).Yo le escribiría a algún especialista en miocardiopatías (tal vez a William J. McKenna o a Barry J. Maron???). La verdad no se quienes dominan este tema porque no es mi especialidad. Según me parece haber entendido, la última serie de CHOP fue en Octubre 2009. Todo paciente con CHOP tiene controles ecocardiográficos seriados para detectar toxicidad miocárdica. Que mostraban los ecos de este paciente? Esta miocarditis se dió en un corazón "sano" o con signos de toxicidad previa por la adriamicina?. Ahora está con algún tto quimioterápico? Ahora está en remisión o en empuje de su linfopatía tumoral?.No ha tenido arritmias ventriculares?Sinceramente me llama la atención que no haya tenido arritmias con esa lesión miocárdica tan severa. Si arranca con una tormenta eléctrica no creo que sobreviva a la misma.

Cordiales saludos y mucha suerte para tu paciente.

Daniel Banina Montevideo, Uruguay

Ante todo muchas gracias por la atención prestada en el caso!!! Elforo tiende a ser muy docente y la verdad estoy muy contentoaprendiendo dia a dia! Bueno con respecto al caso, en el mail inicialfalle en un antecedente de suma importancia! Mas teniendo en cuentalos medicamentos administrados para el linfoma, claro que habia leidoun excelente articulo publicado en la revista de la FAC "toxicidadmiocardica por antraciclinas" escrito por el Dr. Antonio Pasca! Dondedescribe la toxicidad aguda y la cronica la cual se hace evidente hasta 245 dias trascurridos de la ultima dosis (en el presente caso lleva mas de 600 dias de la ultima dosis) con el farmaco mas termible eso si: doxorrubicina!! Ademas describe la afectacion cronica mas como una miocardiopatia degenerativa que va llevando a insuficienciacardiaca cronica congestiva!!tanto de tipo dilatada aunque en algunospacientes restrictiva endomiocardica!! Mas no describen hallazgos como los del presente caso: una miocardiopatia aguda fulminante!!!Tambien hace mencion al tratamiento preventivo con quelantes tipo EDTAcomo dexrazone (el mejor hasta el momento) y otros como verapamilo otitular dosis de el citotoxico!!!Por otro lado el paciente no es VIH positivo! Y la recaida en estecaso estaba por verse, no es muy clara! Ya que un tac con captacion dela tomografia con emision de positrones (pet tac) no siempre essinonimo de neoplasia! Mas cuando el tamaño no es tan significatico!Una simples adenopatias reactivas pueden captar! Por lo que nosenfrentamos ante una cuestion etica con este paciente y los dosservicios! En cuanto a si debe o no ir a trasplante!!Muchas gracias por los articulos! Y espero seguir por mucho tiempodisfrutando de tan alto nivel cardiologico que se vive en este foro!Pues en mi segundo año de residencia estoy cada vez mas convencido quedeseo mi fellowship en cardiologia!!! Un fuerte abrazo
Jonathan

CARDIAC SIDE EFFECTS OF CHEMOTHERAPY

Chemotherapy side effects may include an increased risk of heart disease, especially cardiomyopathy. Certain types of chemotherapy also increase the risk of heart attack, especially during infusion of the medication. Fortunately, heart disease associated with chemotherapy is relatively rare — and not all chemotherapy drugs carry the potential side effect of heart damage.

During treatment, it is necessary periodic heart monitoring. If the patient have a pre-existing heart condition, such as cardiomyopathy, is possible suggest a different type of chemotherapy.

Doxorubicin (trade name **Adriamycin**) is a commonly used chemotherapy agent that is very effective in both Hodgkin and Non-Hodgkin lymphomas. It is used in virtually all the first-line chemotherapy regimens for lymphomas. It belongs to the class of chemotherapy drugs called **anthracyclines.** It is well recognized that doxorubicin may cause damage to the heart in some individuals. While other anthracyclines (like epirubucun and mitoxantrone) may also cause heart damage, the chances are more common with doxorubicin. Doxorubicin causes both early and late heart damage (also called 'cardiotoxicity'). The early damage occurs immediately after drug administration or within 1 to 2 days. There are minor effects that are picked up on the ECG and in most cases resolve without casing any major problems. It is the late-starting damage that is important and more serious. Generally, the risk of heart disease associated with certain chemotherapy drugs increases with the total lifetime amount of the drug you receive. To minimize the risk of heart damage, it is necessary will carefully monitor the amount of each type of chemotherapy drug you receive. If shortness of breath with minimal exertion or chest pain during chemotherapy is present, it is necessary to report it immediately to care team. In addition, some cancers require radiation therapy. If the area of the body receiving radiation includes the heart, increased risk of cardiomyopathy, coronary artery disease and heart attack. The combination of radiation and chemotherapy can further increase the risk of heart damage. Doxorubicin (trade name Adriamycin) is a commonly used chemotherapy agent that is very effective in both Hodgkin and Non-Hodgkin lymphomas. It is used in virtually all the first-line chemotherapy regimens for lymphomas. It belongs to the class of chemotherapy drugs called anthracyclines.

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Late damage to the heart starts about a year or more after chemotherapy. Doxorubicin mainly affects the heart muscles. It weakens the heart muscles and makes the pumping of blood more difficult for the heart. When severe, it leads to a condition called congestive heart failure(CHF). Individuals with CHF complain of a number of symptoms

a gradually worsening difficulty in strenuous work, leading to tiredness or breathing trouble when climbing stairs or walking

a cough that worsens at night

swelling of the feet

difficulty in breathing at rest

If severe, CHF can cause severe disability and even death.

Doxorubicin reacts with some chemicals in the body (called enzymes) to produce harmful substances called free radicals. The production of these harmful free radicals is enhanced in organs like the heart where there is more oxygen and iron. While some organs have special enzymes to destroy these free radicals, the heart has a relatively poor supply of these enzymes. This makes the heart muscles susceptible to damage with free radicals.

Numerous factors increase the chances of heart damage with doxorubicin

A high dose of doxorubicin is most important. The total dose of doxorubicin received during a person's life should be ideally less than 400mg per square meter (of the body surface). The risk of CHF with this dose is less than 1 percent. At higher doses, the chances of heart damage increase. Fortunately, most chemo schedules require lower doses.

The simultaneous use of other chemotherapy drugs that affect the heart e.g. high doses of cyclophosphamide

Radiation treatment to the chest

Already-existing heart disease

Younger age
Female patients
Accumulating evidence shows that obesity is associated with doxorubicin cardiac toxicity in the heart, but the molecular mechanisms that contribute to this pathological response are not understood. Heart damage is usually tested with an echocardiogram (commonly called an 'echo') or a MUGA scan to test for the amount of blood that the heart can pump out. In medical terms, this is called the ‘left ventricular ejection fraction’ or LVEF. The LVEF is measured for most individuals before starting treatment to rule out any pre-existing heart problem. Subsequently, it may be measured again during treatment and later periodically to see if there is a fall in the LVEF. Occasionally cardiac problems can show in the ECG as well.
There are some ways in which heart damage can be prevented or lessened
Keeping the total dose of doxorubicin within safe limits
Administering the drug as an infusion in saline rather than as an injection
Using a new preparation of doxorubicin called ‘liposomal doxorubicin’ - the drug comes enclosed in a fatty coating called a liposome. This coating breaks only within the cancer to release the drug. Normal organs like the heart are less affected.
Using a substance called dexrazoxane as an infusion soon after doxorubicin. It may reduce the chances of heart damage and is FDA approved in metastatic breast cancer.
Mice treated with both HO-3867 and doxorubicin showed significant improvement in cardiac functional parameters when compared to mice treated with doxorubicin alone. Reduced expression of Bcl-2 and pAkt was observed in mice treated with doxorubicin alone, while mice given combination treatment showed levels similar to control. The study indicates that combination treatment of HO-3867 and doxorubicin is a viable option for treatment of cancer with reduced cardiotoxic side effects.

1. **Dayton A, Selvendiran K, Meduru S, et al. Amelioration of doxorubicin-induced cardiotoxicity by an anticancer-antioxidant dual-function compound, HO-3867. J Pharmacol Exp Ther. 2011 Jul 28. [Epub ahead of print]**

Adiponectin ameliorates doxorubicin-induced cardiotoxicity through an Akt dependent Maruyama investigated the effect of adiponectin on doxorubicin (doxorubicin)-induced cardiotoxicity and assessed the mechanisms of this effect. A single dose of doxorubicin was intraperitoneally injected into abdomen of adiponectin-knockout (APN-KO) and wild-type (WT) mice. APN-KO mice had increased mortality and exacerbated contractile dysfunction of left ventricle (LV) compared with WT mice. APN-KO mice also showed increased apoptotic activity and diminished Akt signaling in the failing myocardium. Systemic delivery of adenoviral vector expressing adiponectin improved LV dysfunction and myocardial apoptosis following doxorubicin injection in WT and APN-KO mice, but not in Akt1 heterozygous KO mice. In cultured rat neonatal cardiomyocytes, adiponectin stimulated Akt phosphorylation and inhibited doxorubicin -stimulated apoptosis. Treatment with sphingosine kinase-1 inhibitor or sphingosine-1 phosphate receptor antagonist diminished adiponectin-indu ced Akt phosphorylation and reversed the inhibitory effects of adiponectin on myocyte apoptosis. Pretreatment with anti-calreticulin antibody reduced the binding of adiponectin to cardiac myocytes and blocked adiponectin-stimulated increase in Akt activation and survival in cardiomyocytes. Interference of the LRP1/calreticulin co-receptor system by siRNA or blocking antibodies diminished the stimulatory actions of adiponectin on Akt activation and myocyte survival. These data show that adiponectin protects against doxorubicin -induced cardiotoxicity by its ability to promote Akt signaling.

1. **Maruyama S, Shibata R, Ohashi K, et al. Adiponectin ameliorates doxorubicin-induced cardiotoxicity through an Akt dependent mechanism. Biol Chem. 2011 Jul 22. [Epub ahead of print]mechanism. Biol Chem. 2011 Jul 22. [Epub ahead of print]**

HF caused by **doxorubicin** is treated on the same lines as other types of HF. There are no special medicines for doxorubicin related heart damage. Rest, oxygen and pills reduce the symptoms of CCF and stabilize the cardiac disability. Severe symptoms may require hospital admission.

Doxorubicin is an extremely effective chemotherapy drug. It has a role in the treatment of many cancers. While there is a definite association of doxorubicin with heart damage, the benefits of using doxorubicin outweigh the risks. Heart damage with this drug is quite well understood, and if doxorubicin is used within the safe dose limits, there is no reason to stop using a drug as useful as this.

Heart disease due to the drug doxorubicin a potent broad-spectrum antitumor agent effective in treating a variety of cancers including solid tumors and leukemia. Unfortunately, its clinical use is limited by dose-dependent cardiac side effects that lead to degenerative cardiomyopathy, CHF, and death. In addition, some adult patients treated with the drug when they were children later develop dilated cardiomyopathy.

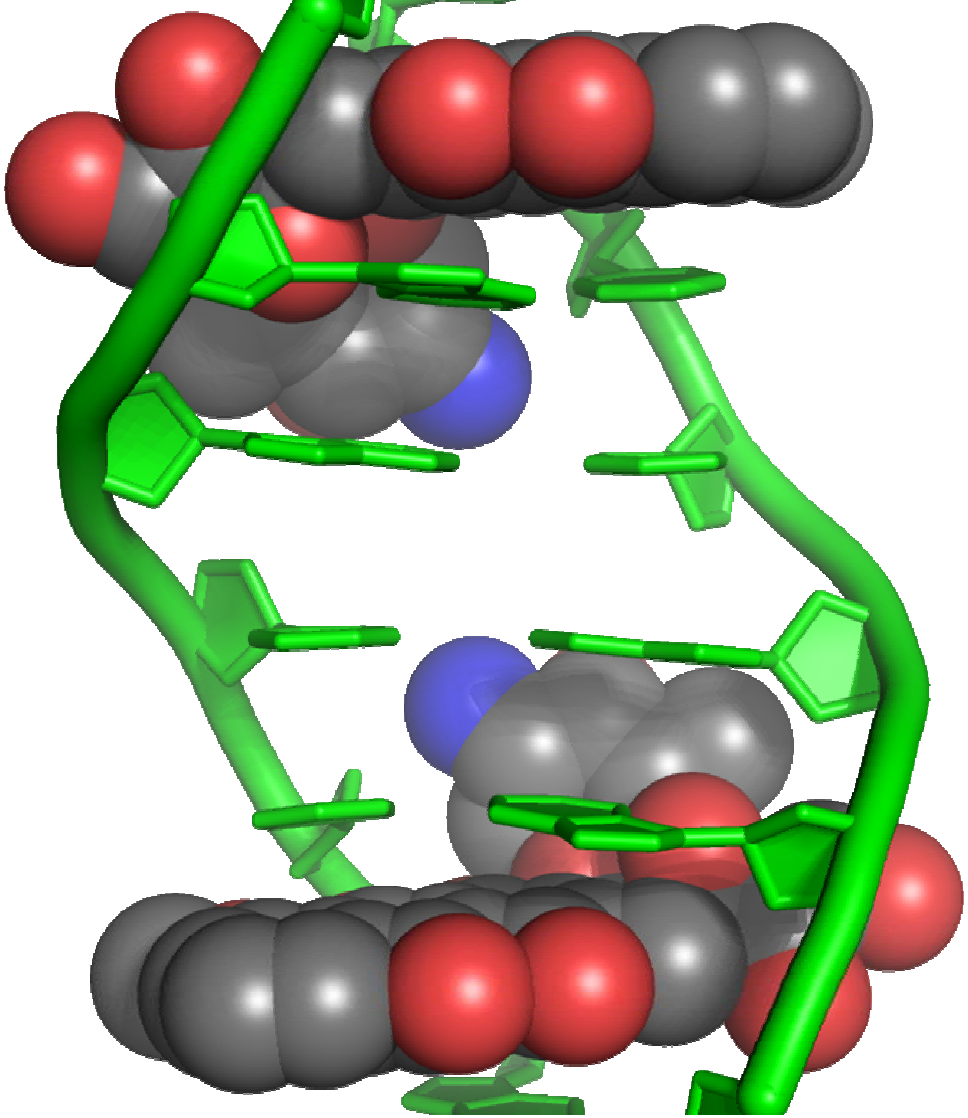
Endocardial biopsies from patients undergoing doxorubicin therapy reveal a **disruption of myofibrils, impairment of microtubule assembly, and a swelling of the endoplasmic reticulum.** Doxorubicin cardiotoxicity is also characterized by a dose-dependent decline in mitochondrial oxidative phosphorylationand a decrease in high-energy phosphate pools.

Established doxorubicin cardiomyopathy is a lethal disease. When congestive heart failure develops, mortality is approximately 50%. Extensive research has been done to understand the mechanism and pathophysiology of doxorubicin cardiomyopathy, and considerable knowledge and experience has been gained. Unfortunately, no effective treatment for established doxorubicin cardiomyopathy is presently available. Extensive research has been done and is being done to discover preventive treatments. However an effective and clinically applicable preventive treatment is yet to be discovered.

The exact mechanism of action of doxorubicin is complex and still somewhat unclear, however Doxorubicin is known to interact with DNA by intercalation and inhibition of macromolecular biosynthesis[1]. This inhibits the progression of the enzyme topoisomerase II, which relaxes supercoils in DNA for transcription. Doxorubicin stabilizes the topoisomerase II complex after it has broken the DNA chain for replication, preventing the DNA double helix from being resealed and thereby stopping the process of replication.

The planar aromatic chromophore portion of the molecule intercalates between two base pairs of the DNA, while the six-membered daunosamine sugar sits in the minor groove and interacts with flanking base pairs immediately adjacent to the intercalation site, as evidenced by several crystal structures.2225

1. **Fornari FA, Randolph JK, Yalowich JC, et al. Interference by doxorubicin with DNA unwinding in MCF-7 breast tumor cells.Mol Pharmacol. 1994 Apr;45(4):649-56.**



Cartoon diagram of two doxorubicin molecules intercalating DNA, from PDB

The anticancer drugs adriamycin and daunomycin have each been crystallized with the DNA sequence d(CGATCG) and the three-dimensional structures of the complexes solved at 1.7- and 1.5-A resolution, respectively. These antitumor drugs have significantly different clinical properties, yet they differ chemically by only the additional hydroxyl at C14 of adriamycin. In these complexes the chromophore is intercalated at the CpG steps at either end of the DNA helix with the amino sugar extended into the minor groove. Solution of the structure of daunomycin bound to d(CGATCG) has made it possible to compare it with the previously reported structure of daunomycin bound to d(CGTACG). Although the two daunomycin complexes are similar, there is an interesting sequence dependence of the binding of the amino sugar to the A-T base pair outside the intercalation site. The complex of daunomycin with d(CGATCG) has tighter binding than the complex with d(CGTACG),. The structures of daunomycin and adriamycin with d(CGATCG) are very similar. However, there are additional solvent interactions with the adriamycin C14 hydroxyl linking it to the DNA. Surprisingly, under the influence of the altered solvation, there is considerable difference in the conformation of spermine in these two complexes. The observed changes in the overall structures of the ternary complexes amplify the small chemical differences between these two antibiotics and provide a possible explanation for the significantly different clinical activities of these important drugs[1].

1. **Frederick CA, Williams LD, Ughetto G, et al . Structural comparison of anticancer drug-DNA complexes: adriamycin and daunomycin. Biochemistry. 1990 Mar 13;29(10):2538-49.**

ANTHRACYCLINES/ANTHRAQUINOLONES

Anthracyclines are the best studied of the anticancer drugs with established cardiotoxicity. The Food and Drug Administration–approved anthracyclines, doxorubicin, daunorubicin,**1** and epirubicin,**2** are used to treat many hematologic and solid malignancies. Acute cardiotoxicity may manifest as nonspecific ST-segment and T-wave abnormalities. In contrast to early effects, late anthracycline cardiotoxicity is cumulative, dose related, and, at sufficiently high dosages, can result in CHF and LV dysfunction. The mechanism is thought to be direct myocardial injury due to formation of free radicals.**3**

The prevalence of cardiomyopathy increases significantly when patients are given doses of doxorubicin >550 mg/m2. However, more recent studies have shown that lower cumulative doses can cause similar cardiomyopathy.[4]

The mortality rate among patients who actually develop late cardiotoxicity has been estimated to be high[5], but the dismal prognosis can be greatly altered by early recognition and treatment. Mitoxantrone, a derivative of the anthracyclines, can cause mild cardiotoxicity that is similar to that caused by anthracyclines at currently used dosages[6].

1. **Von Hoff DD, Rozencweig M, Layard M,et al. Daunomycin-induced cardiotoxicity in children and adults. A review of 110 cases.Am J Med. 1977 Feb;62(2):200-8.**
2. ***Torti FM, Bristow MM, Lum BL, et al. Cardiotoxicity of epirubicin and doxorubicin: assessment by endomyocardial biopsy. Cancer Res. 1986; 46: 3722–3727.***
3. ***Myers C. Role of iron in anthracycline action. In: Hacker M, Lazo J, Tritton T, eds. Organ Directed Toxicities of Anticancer Drugs. Boston, Mass: Martinus Nijhoff; 1988: 17–30***
4. ***Swain SM, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. Cancer. 2003; 97: 2869–2879.***
5. ***Ali MK. The natural history of anthracycline cardiotoxicity in children. In: Muggia F, ed. Cancer Treatment and the Patient. Baltimore, Md: The Johns Hopkins University; 1992: 246–255.***
6. ***Benjamin RS. Rationale for the use of mitoxantrone in the older patient: cardiac toxicity. Semin Oncol. 1995; 22: 11–13.***

ALKYLATING

Another commonly used class of chemotherapy agents is the alkylators, first used in the treatment of leukemia. A few cases of pericardial and endomyocardial fibrosis occurring 4 to 9 years after busulfan treatment have been reported, but the cumulative doses in these cases usually exceeded 600 mg[1]. Cyclophosphamide has been used in combination chemotherapy for several solid tumors and lymphomas. Although cyclophosphamide is relatively well tolerated at lower doses, high-dose regimens such as those given with bone marrow transplantation can be associated with a variety of adverse effects[2]. However, the total dose of an individual course, rather than the cumulative dose, seems to be the best predictor of acute cardiotoxicity[3]. Prior treatment with an anthracycline and mediastinal radiation therapy have also been proposed as contributing factors[4].Subsequent cardiac adverse events may include HF, myocarditis, or pericarditis[5]. Gross changes at autopsy have included increased LV wall thickness with hemorrhagic myocardial necrosis[3] The mechanism of injury is thought to be related to endothelial and myocyte injury mediated through a toxic metabolite[6]. Acute toxic effects can last up to 6 days, but long-term effects are not usually seen in those who survive[2]. Cyclophosphamide has been reported to cause cardiac necrosis resulting in the acute or subacute development of CHF. This has been seen in some patients after the use of very high does (120-140mg/kg) in preparation for bone marrow transplant. Cyclophosphamide as well as the VINCA ALKALOIDS have also been reported to cause ischemic cardiac toxicity.

1. ***Terpstra W, de Maat CE. Pericardial fibrosis following busulfan treatment. Neth J Med. 1989; 35: 249–252.***
2. ***Gottdiener JS, Appelbaum FR, Ferrans VJ, et al. Cardiotoxicity associated with high-dose cyclophosphamide therapy. Arch Intern Med. 1981; 141: 758–763.***
3. ***Dow E, Schulman H, Agura E. Cyclophosphamide cardiac injury mimicking acute myocardial infarction. Bone Marrow Transplant. 1993; 12: 169–172.***
4. ***Steinherz LJ, Steinherz PG, Mangiacasale D, et al. Cardiac changes with cyclophosphamide. Med Pediatr Oncol. 1981; 9: 417–422.***
5. ***Braverman AC, Antin JH, Plappert MT, et al. Cyclophosphamide cardiotoxicity in bone marrow transplantation: a prospective evaluation of new dosing regimens. J Clin Oncol. 1991; 10: 995–1000.***
6. ***Kupari M, Volin L, Suokas A, et al. Cardiac involvement in bone marrow transplantation: electrocardiographic changes, arrhythmias, heart failure and autopsy findings. Bone Marrow Transplant. 1990; 5: 91–98.***

Quezado et al[1] reported a significant, dose-related incidence of HF and arrhythmia in patients given ifosfamide. All of the patients who died were found to have increased heart weight and small pericardial effusions at autopsy; less common findings were subendocardial hemorrhage and petechial lesions in the epicardium.

Acute clinical syndromes associated with cisplatin infusion include chest pain, palpitations, and, evenetually, elevated cardiac enzymes indicative of MI[2]. A subset of patients receiving cisplatin in combination with cyclophosphamide have developed HF; the risk was greatest among those of advanced age or with prior mediastinal irradiation[3]. Cisplatin is unique in that it can cause late cardiovascular complications such as hypertension, LVH, myocardial ischemia, and MI as long as 10 to 20 years after the remission of metastatic testicular cancer[4].Nephrotoxicity, experienced by up to 35% of patients receiving cisplatin, can lead to significant hypomagnesemia and hypokalemia, which in turn can cause cardiac arrhythmias.

Mitomycin has been used in the treatment of many solid tumors. It has been associated with the development of cardiomyopathy, especially when administered with or after an anthracycline[5]. A cumulative dose effect has been suggested, with complications appearing later in the course of treatment. Superoxide radicals form when mitomycin is reduced to a semiquinone radical under aerobic conditions[6], and this process may play a role in the development of cardiotoxic effects.

1.Quezado ZM, Wilson WH, Cunnion RE, et al. High-dose ifosfamide is associated with severe, reversible cardiac dysfunction. Ann Intern Med. 1993; 118: 31–36.

2.Berliner S, Rahima M, Sidi Y, et al. Acute coronary events following cisplatin-based chemotherapy. Cancer Invest. 1990; 8: 583–586.

3.Nieto Y, Cagnoni P, Bearman SI, et al. Cardiac toxicity following high-dose cyclophosphamide, cisplatin, and BCNU (STAMP-I) for breast cancer. Biol Blood Marrow Transplant. 2000; 6: 198–203.

4.Meinardi MT, Gietema JA, van der Graaf WT, et al. Cardiovascular morbidity in long-term survivors of metastatic testicular cancer. J Clin Oncol. 2000; 18: 1725–1732.

5.Buzdar AU, Legha SS, Tashima CK, et al. Adriamycin and mitomycin C: possible synergistic cardiotoxicity. Cancer Treat Rep. 1978; 62: 1005–1008.

6.Tomasz M, Mercado CM, Olson J, et al. The mode of interaction of mitomycin C with deoxyribonucleic acid and other polynucleotides in vitro. Biochemistry. 1974; 13: 4878–4887.

ANTIMETABOLITES

The chemotherapeutic agent **5-fluorouracil (5-FU)** is widely used in the treatment of many solid tumor treatment protocols. The most commonly described cardiotoxic effect is the ischemic syndrome[1], which varies clinically from angina pectoris to acute MI. A “rechallenge” with 5-fluorouracil frequently reproduces the clinical cardiotoxicity. The ischemia is usually reversible on cessation of the 5-fluorouracil and implementation of anti-ischemic medical therapy. Ischemia can occur in patients without underlying CAD (incidence, 1.1%), but the incidence is higher in patients with CAD (4.5%)[2]. 5-FU has been implicated as a cause of cardiotoxicity. The toxicity manifests as ischemic pain within hours of a dose. MI has been reported. ECG changes consistent with ischemia and response/prevention with nitrates have been noted. The toxicity is not clearly dose related, although it has been suggested that the incidence is considerably higher when 5-FU is given as a continuous infusion rather than a bolus (10% versus about 1%). Some patients have received further treatment safely, but the need for 5-FU in the face of cardiotoxicity may obviously be re-evaluated.

Capecitabine is currently used in the treatment of breast and gastrointestinal cancers and is believed to be less toxic than 5-fluorouracil . Other reported cardiotoxic effects associated with capecitabine include angina or MI[3], arrhythmias, ECG changes, and cardiomyopathy.

1. ***Gradishar WJ, Vokes EE. 5-Fluorouracil cardiotoxicity: a critical review. Ann Oncol. 1990; 1: 409–414.***
2. ***Labianca R, Beretta G, Clerici M, et al. Cardiac toxicity of 5-fluorouracil: a study on 1083 patients. Tumori. 1982; 68: 505–510.***
3. ***Frickhofen N, Beck FJ, Jung B, et al. Capecitabine can induce acute coronary syndrome similar to 5-fluorouracil. Ann Oncol. 2002; 13: 797–801.***

ANTIMICROTUBULE AGENTS

Paclitaxel is used extensively in the treatment of many solid tumors and has recently been used to coat stents for cardiovascular use. It has been reported to cause sinus bradycardia, heart block, PVCs, and VT[1].
Thrombosis has also been reported with the use of paclitaxel[2]. In a large study of approximately 1000 patients, the incidence of cardiac toxicity was 14%[3], and most incidents (76%) were grade I asymptomatic bradycardia[3].

Vinca alkaloids are used primarily in the treatment of leukemia and lymphoma. They have been reported to cause autonomic neuropathy[4], angina[5], myocardial ischemia and MI[6].
Vinorelbine-related cardiac events are more likely to occur in women than in men[7]. The occasional clinical presentation of Prinzmetal's angina and reversible ECG changes has led to the hypothesis of ischemia induced by coronary spasm[5].

1. ***Rowinsky EK, McGuire WP, Guarnieri T, et al. Cardiac disturbances during the administration of Taxol. J Clin Oncol. 1991; 9: 1704–1712.***
2. ***Sevelda P, Mayerhofer K, Obermair A, et al. Thrombosis with paclitaxel. Lancet. 1994; 343: 727.***
3. ***Trimble EL, Adams JD, Vena D, et al. Paclitaxel for platinum-refractory ovarian cancer: results from the first 1,000 patients registered to National Cancer Institute Treatment Referral Center 9103. J Clin Oncol. 1993; 11: 2405–2410.***
4. ***Roca E, Bruera E, Politi PM, et al. Vinca alkaloid–induced cardiovascular autonomic neuropathy. Cancer Treat Rep. 1985; 69: 149–151.***
5. ***Yancey RS, Talpaz M. Vindesine-associated angina and ECG changes. Cancer Treat Rep. 1982; 66: 587–589.***
6. ***Lejonc JL, Vernant JP, Macquin J, et al. Myocardial infarction following vinblastine treatment. Lancet. 1980; 2: 692.***
7. ***Lapeyre-Mestre M, Gregoire N, Bugat R, et al. Vinorelbine-related cardiac events: a meta-analysis of randomized clinical trials. Fundam Clin Pharmacol. 2004; 18: 97–105.***

MONOCLONAL ANTIBODIES

Advances in cancer therapy have led to the use of monoclonal antibodies to manage certain hematologic malignancies and solid tumors[1] Infusion of these agents commonly causes hypotension caused by the massive release of cytokines, as well as fever, dyspnea, hypoxia, or even death[2]. However, they also have unique toxicity profiles specific to the receptors they block.

Alemtuzumab has been associated with infusion-related reactions including hypotension, bronchospasm, and rash, usually during the first week of therapy. LV dysfunction is rare but has been reported in patients with cutaneous T-cell lymphoma who had previously undergone multiple chemotherapy regimens[3]. Careful monitoring for hypotension is recommended for patients with preexisting cardiac disease. Antihistamines, acetaminophen, steroids, and slow infusions have all been used to prevent or treat the infusion reactions.

Pexelizumab may be hazardous to those with ST-segment elevation MI undergoing primary percutaneous interventions without using glycoprotein IIb-IIIa inhibitors[4].
Cardiologists and oncologists should collaborate with the aim of balancing the risks of cardiotoxicity with the benefits of oncologic therapy[5].

1. ***Mellstedt H. Monoclonal antibodies in human cancer. Drugs Today (Barc). 2003; 39 (suppl C): 1–16.***
2. ***Albanell J, Baselga J. Systemic therapy emergencies. Semin Oncol. 2000; 27: 347–361.***
3. ***Lenihan DJ, Alencar AJ, Yang D, et al. Cardiac toxicity of alemtuzumab in patients with mycosis fungoides/Sézary syndrome. Blood. 2004 Aug 1;104(3):655-8.***
4. ***Lin GM Chu KM, Han CL. Pexelizumab may be hazardous to those with ST-segment elevation myocardial infarction undergoing primary percutaneous interventions without using glycoprotein IIb-IIIa inhibitors. Int J Cardiol. 2011 Jan 21;146(2):280-2.***
5. ***Ewer MS, Ewer SM. Cardiotoxicity of anticancer treatments: what the cardiologist needs to know. Nat Rev Cardiol. 2010 Oct;7(10):564-75.***

Bevacizumab[1], a humanized monoclonal IgG1 antibody that binds to and inhibits the activity of human vascular endothelial growth factor, was recently approved for use in combination with 5-FU–based therapy for metastatic colorectal carcinoma. Newly developed or worsening hypertension is a commonly observed side effect. In clinical trials, severe hypertension occurred in up to 5% of patients, with rare cases of hypertensive crises of encephalopathy and subarachnoid hemorrhage. In patients previously given anthracyclines or with a history of left chest wall irradiation, the incidence of CHF was 4%, and this incidence increased to 14% in patients undergoing concurrent anthracycline therapy[2;3].

Cetuximab, a human/mouse chimeric monoclonal antibody that binds to the human epidermal growth factor receptor, has been approved for treatment of metastatic colorectal carcinoma with or without irinotecan. Severe, potentially fatal infusion reactions characterized by bronchospasm, urticaria, and hypotension have been noted in approximately 3% of patients[4]. Rare cases of interstitial pneumonitis with noncardiogenic pulmonary edema have also been reported[5.]

Rituximab, a chimeric murine/human monoclonal antibody against the CD20 antigen, is used in a wide spectrum of non-Hodgkin lymphoma. Most of the side effects of rituximab are infusion related and occur within the first few hours, especially during the first infusion. Less severe reactions such as hypotension, angioedema, hypoxia, or bronchospasm can be seen in up to 10% of cases. Supportive care measures including intravenous fluids, vasopressors, bronchodilators, diphenhydramine, and acetaminophen are usually effective[6].

1. ***Avastin (bevacizumab) [package insert]. South San Francisco, Calif: Genentech, Inc; 2004.***
2. ***Cobleigh MA, Langmuir VK, Sledge GW, et al. A phase I/II dose-escalation trial of bevacizumab in previously treated metastatic breast cancer. Semin Oncol. 2003; 30: 117–124***
3. ***Raghavan D, Cox K, Childs A, et al. Hypercholesterolemia after chemotherapy for testis cancer. J Clin Oncol. 1992; 10: 1386–1389.***
4. ***Saltz LB, Meropol NJ, Loehrer PJ Sr, et al. Phase II trial of cetuximab in patients with refractory colorectal cancer that expresses the epidermal growth factor receptor. J Clin Oncol. 2004; 22: 1201–1208.***
5. ***Needle MN. Safety experience with IMC-C225, an anti-epidermal growth factor receptor antibody. Semin Oncol. 2002; 29: 55–60.***
6. ***Cersosimo RJ. Monoclonal antibodies in the treatment of cancer, part 2. Am J Health Syst Pharm. 2003; 60: 1631–1641;quiz 1642–1643.***

Trastuzumab,another recombinant humanized IgG1 monoclonal antibody that selectively binds to the human epidermal growth factor receptor 2 protein (HER2), has been approved for the treatment of breast cancer that overexpresses HER2, a variant that accounts for approximately 25% to 30% of breast cancer cases and is associated with a poorer prognosis[1]. The reported incidence of cardiac dysfunction and CHF with trastuzumab has been higher than anticipated, especially when it is used in combination with other cardiotoxic chemotherapy[2]. Preexisting cardiac disease, older age, prior cardiotoxic therapy, and radiation to the chest may increase the incidence of cardiotoxicity. However, the true incidence of trastuzumab-induced cardiac dysfunction is not clearly defined. In the initial clinical trials of trastuzumab, use of this agent alone was associated with up to a 2% risk of developing significant cardiac dysfunction (NYHA class III to IV HF) and increased to 16% when trastuzumab was used in combination with anthracyclines and cyclophosphamide[2]. In more recent trials, monitoring LV function before and during treatment and not administering these drugs simultaneously have substantially reduced toxicity[3]. The mechanism responsible for the cardiac dysfunction is not known but has been shown to be different from that of doxorubicin and may be secondary to a sequential stress mechanism[4]. Animal data have suggested that signaling through HER2 in cardiac myocytes is essential for the prevention of dilated cardiomyopathy[5].

1. ***Slamon DJ, Clark GM, Wong SG, et al. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science. 1987; 235: 177–182.***
2. ***Seidman A, Hudis C, Pierri MK, et al. Cardiac dysfunction in the trastuzumab clinical trials experience. J Clin Oncol. 2002; 20: 1215–1221.***
3. ***Perez EA, Rodeheffer R. Clinical cardiac tolerability of trastuzumab. J Clin Oncol. 2004; 22: 322–329.***
4. ***Ewer MS, Gibbs HR, Swafford J, et al. Cardiotoxicity in patients receiving transtuzumab (Herceptin): primary toxicity, synergistic or sequential stress, or surveillance artifact? Semin Oncol. 1999; 26: 96–101.***
5. ***Crone SA, Zhao YY, Fan L, et al. ErbB2 is essential in the prevention of dilated cardiomyopathy. Nat Med. 2002; 8: 459–465.***

INTERLEUKINS

Interleukin-2 (IL-2), a T-cell growth factor, has been approved for the treatment of metastatic renal cell carcinoma and melanoma. High-dose IL-2 treatment results in adverse cardiovascular and hemodynamic effects similar to septic shock[1] and can lead to hypotension, vascular leak syndrome, and respiratory insufficiency requiring pressors and mechanical ventilation support[2]. Severe cases may result in cardiac arrhythmias, MI, cardiomyopathy, and myocarditis[3]. Improvements in patient selection and treatment protocols have substantially reduced IL-2 treatment–related toxicity[4]. Denileukin diftitox (Ontak), an IL-2/diphtheria toxin fusion protein, is used in the treatment of T-cell lymphoma. It can cause vascular leak syndrome (hypotension, edema, hypoalbuminemia), as well as dyspnea, chest pain, dizziness, and syncope. Slowing or terminating the infusion and administering antihistamines, steroids, and epinephrine can relieve these reactions[5]. Premedication with steroids can also prevent or ameliorate acute infusion events[6]. Thrombotic events such as deep vein thrombosis, pulmonary embolism, and arterial thrombosis have been reported in approximately 11% of patients[7].

1. ***Vial T, Descotes J. Immune-mediated side-effects of cytokines in humans. Toxicology. 1995; 105: 31–57.***
2. ***White RL Jr, Schwartzentruber DJ, Guleria A, et al. Cardiopulmonary toxicity of treatment with high dose interleukin-2 in 199 consecutive patients with metastatic melanoma or renal cell carcinoma. Cancer. 1994; 74: 3212–3222***
3. ***Nora R, Abrams JS, Tait NS, et al. Myocardial toxic effects during recombinant interleukin-2 therapy. J Natl Cancer Inst. 1989; 81: 59–63.***
4. ***Kammula US, White DE, Rosenberg SA. Trends in the safety of high dose bolus interleukin-2 administration in patients with metastatic cancer. Cancer. 1998; 83: 797–805.***
5. ***Railan D, Fivenson DP, Wittenberg G. Capillary leak syndrome in a patient treated with interleukin 2 fusion toxin for cutaneous T-cell lymphoma. J Am Acad Dermatol. 2000; 43: 323–324.***
6. ***Foss FM, Bacha P, Osann KE, et al. Biological correlates of acute hypersensitivity events with DAB(389)IL-2 (denileukin diftitox, ONTAK) in cutaneous T-cell lymphoma: decreased frequency and severity with steroid premedication. Clin Lymphoma. 2001; 1: 298–302.***
7. ***Olsen E, Duvic M, Frankel A, et al. Pivotal phase III trial of two dose levels of denileukin diftitox for the treatment of cutaneous T-cell lymphoma. J Clin Oncol. 2001; 19: 376–388.***

INTERFERONS

Interferon-α is produced by macrophages and lymphocytes and has been approved for the treatment of many types of cancer. Interferons usually cause acute symptoms during the first 2 to 8 hours after treatment, including flu-like symptoms, hypotension or hypertension, tachycardia, and nausea and vomiting[1]. In severe cases, angina and MI have been reported.

The combination of pegylated interferon (PEG-IFN) and ribavirin (RBV) is the current treatment for chronic hepatitis C (CHC). The treatment is thought to suppress viral replication and induce viral clearance via immunomodulatory effects. For this reason, concern exists for the use of this treatment in recipients of a solid organ transplantation. In heart transplant recipients with CHC. Treatment with PEG-IFN/RBV may be safely offered to stable heart transplant recipients with CHC and signs of liver disease progression. Close monitoring of treatment safety is mandatory[2].

PENTOSTATIN

Pentostatin, a purine analogue used in the treatment of hairy cell leukemia and other hematologic malignancies, may have several cardiotoxic effects[3],including MI, CHF, and arrhythmias[4]. Cardiotoxicity is particularly prominent when pentostatin is given with high doses of cyclophosphamide in preparation for bone marrow transplantation[5].

1. ***Vial T, Descotes J. Immune-mediated side-effects of cytokines in humans. Toxicology. 1995; 105: 31–57.***
2. ***Durante-Mangoni E, Ragone E, Pinto D, et al. Outcome of treatment with pegylated interferon and ribavirin in heart transplant recipients with chronic hepatitis C. Transplant Proc. 2011 Jan-Feb;43(1):299-303.***
3. ***Pai VB, Nahata MC. Cardiotoxicity of chemotherapeutic agents: incidence, treatment and prevention. Drug Saf. 2000; 22: 263–302.***
4. ***Grem JL, King SA, Chun HG, et al. Cardiac complications observed in elderly patients following 2'-deoxycoformycin therapy. Am J Hematol. 1991; 38: 245–247.***
5. ***Gryn J, Gordon R, Bapat A, et al. Pentostatin increases the acute toxicity of high dose cyclophosphamide. Bone Marrow Transplant. 1993; 12: 217–220.***

HOMOHARRINGTONINE

Homoharringtonine, most often used in the treatment of leukemia, can be associated with severe hypotension—a dose-related and occasionally rate-limiting effect that may be related to its calcium channel–blocking activity[1]. PVCs, ventricular tachycardia, and AF have been reported after administration of homoharringtonine[2].

ETOPOSIDE

Etoposide is used mainly in the treatment of refractory testicular tumors and small-cell lung carcinoma. The most common cardiac side effect is hypotension[3], although myocardial ischemia and MI have also been noted.72 Patients who have previously undergone chemotherapy or mediastinal radiation may be at increased risk for MI after etoposide treatment[4],and concomitant chemotherapy with other agents may also be a predisposing factor for MI[5].

MITOXANTRONE

is associated with cardiomyopathy, especially in patients who have received previous doxorubicin, but the incidence is less than that seen with doxorubicin. Cumulative dose recommendations for minimizing the occurrence of cardiomyopathy are 160mg/m2 in patients without prior doxorubicin and 100mg/m2 in patients with prior doxorubicin. These cutoffs are also viewed in light of the patients underlying disease and the need for continued drug. (approximate equivalent doses are 60mg/m2 doxorubicin and 12mg/m2 mitoxantrone)

1. ***Zhou DC, Zittoun R, Marie JP. Homoharringtonine: an effective new natural product in cancer chemotherapy. Bull Cancer. 1995; 82: 987–995.***
2. ***Ajani JA, Dimery I, Chawla SP, et al. Phase II studies of homoharringtonine in patients with advanced malignant melanoma; sarcoma; and head and neck, breast, and colorectal carcinomas. Cancer Treat Rep. 1986; 70: 375–379.***
3. ***Cohen MH, Broder LE, Fossieck BE, et al. Phase II clinical trial of weekly administration of VP-16-213 in small cell bronchogenic carcinoma. Cancer Treat Rep. 1977; 61: 489–490.***
4. ***Airey CL, Dodwell DJ, Joffe JK, et al. Etoposide-related myocardial infarction. Clin Oncol. 1995; 7: 135.***
5. ***Schecter JP, Jones SE, Jackson RA. Myocardial infarction in a 27-year-old woman: possible complication of treatment with VP-16-213 (NSC-141540), mediastinal irradiation, or both. Cancer Chemother Rep. 1975; 59: 887–888.***

ARSENIC TRIOXIDE

Arsenic trioxide is used in the treatment of refractory or relapsed acute promyelocytic leukemia. Arsenic is commonly known to cause ECG abnormalities, producing QT prolongation in >50% of patients[1]. Other side effects include sinus tachycardia, nonspecific ST-T changes, and torsades de pointes.In one study, the most common acute side effect was fluid retention with pleural and pericardial effusions[2].In addition to prolonged QT interval, complete heart block and SCD have also been reported[3]. In these cases, the infusion of arsenic had been completed 7 to 22 hours before the event, underscoring the importance of continuous monitoring after the infusion has been completed[4].

IMATINIB MESYLATE

Imatinib mesylate, an important agent used in the treatment of chronic myelogenous leukemia and other malignancies, is a specific inhibitor of the BCR-ABL tyrosine kinase found in several types of malignant cells. Imatinib mesylate is associated with a significant incidence of edema, which can progress to severe fluid retention and result in pericardial or pleural effusions or generalized third-space fluid accumulation[5].

1. *Soignet SL. Clinical experience of arsenic trioxide in relapsed acute promyelocytic leukemia. Oncologist. 2001; 6 (suppl 2): 11–16.*
2. *Huang SY, Chang CS, Tang JL, et al. Acute and chronic arsenic poisoning associated with treatment of acute promyelocytic leukaemia. Br J Haematol. 1998; 103: 1092–1095.*
3. *Huang CH, Chen WJ, Wu CC, et al. Complete atrioventricular block after arsenic trioxide treatment in an acute promyelocytic leukemic patient. Pacing Clin Electrophysiol. 1999; 22: 965–967.*
4. *Westervelt P, Brown RA, Adkins DR, et al. Sudden death among patients with acute promyelocytic leukemia treated with arsenic trioxide. Blood. 2001; 98: 266–271.*
5. *Kantarjian H, Sawyers C, Hochhaus A, et al. Hematologic and cytogenetic responses to imatinib mesylate in chronic myelogenous leukemia. N Engl J Med. 2002; 346: 645–652.*

Cancer drugs that have been reported to cause abnormalities in HR or rhythm in more than 10% of patients:

1. **Arsenic trioxide (Trisenox®)**
2. **Daunorubicin (Cerubidine®)**
3. **Denileukin diftitox (Ontak®)**
4. **Gemtuzumab ozogamicin (Mylotarg®)**
5. **Idarubicin (Idamycin®)**
6. **Melphalan (Alkeran®)**
7. **Octreotide (Sandostatin®)**
8. **Oprevelkin (Neumega®)**
9. **Paclitaxel (Taxol®)**
10. **Tretinoin (Vesanoid®)**

CARDIOMYOPATHY IN PATIENTS INFECTED WITH THE HUMAN IMMUNODEFICIENCY VIRUS

The cause of cardiomyopathy in patients infected with the human immunodeficiency virus (HIV) remains largely unknown, although a number of predisposing factors have been identified. Malnutrition has been postulated to be a contributory factor, but the association of anthropometric measures of nutritional status with HIV-associated cardiomyopathy has not been established. A lower BMI is associated with cardiomyopathy in people who are living with HIV.Structural and functional abnormalities are prevalent in HIV-infected African children and therefore justify inclusion of routine echocardiography in their standard care. Prevalence of cardiac abnormalities in HIV-infected children was 75.9%. Abnormalities included HF, DCM (33.7%), decreased LVSF of ≤□25% in 33.7%, increased LV mass (20.5%) and pericardial effusion (14.5%). The introduction of highly active antiretroviral therapy (HAART) has generated a contrast in the cardiac manifestations of acquired HIV syndrome. In developed countries, is observed an approximately 30% reduction in the prevalence of (HIV)-associated cardiomyopathy, possibly related to a reduction of opportunistic infections and myocarditis. In developing countries, however, where the availablity of HAART is limited and the pathogenic impact of nutritional factors is significant. In approximately 32% increase in the prevalence of HIV-associated cardiomyopathy and a related high mortality rate from CHF. Also, some HAART regimens in developed countries, especially those including protease inhibitors, have been shown to cause, in a high proportion of HIV-infected patients, an iatrogenic metabolic syndrome (HIV-lipodystrophy syndrome) that is associated with an increased risk of cardiovascular events related to a process of accelerated atherosclerosis, even in young HIV-infected people. Careful cardiac screening is warranted for patients who are being evaluated for, or who are receiving,. A close collaboration between cardiologists and infectious disease specialists is needed for decisions regarding the use of antiretrovirals, for a careful stratification of cardiovascular risk factors, and for cardiovascular monitoring of HIV-infected patients receiving HAART, according the most recent clinical guidelines.

1. **Okoromah CA, Ojo OO, Ogunkunle OO. Cardiovascular Dysfunction in HIV-infected Children in a Sub-Saharan African Country: Comparative Cross-sectional Observational Study. Trop Pediatr. 2011 Feb 3. [In Press]**