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The role of early contrast-enhanced chest computed tomography in the aetiological diagnosis of patients presenting with cardiac tamponade or large pericardial effusion

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Aims The role of chest computed tomography (CT) is not well defined for either diagnosis or management of pericardial disease. The aim of this study was to evaluate the added value of early chest CT in the diagnostic workup for patients presenting with cardiac tamponade or large pericardial effusion of unknown aetiology as the first manifestation of disease.

Methods and results We performed CT scan on 55 patients with pericardial effusion as defined above, undergoing echo-guided pericardiocentesis. We compared the success rate in making diagnosis and/or staging the underlying disorder of three sequential workups, including, respectively, (i) clinical presentation, inflammatory markers, chest X-ray imaging, (ii) all of the above and pericardial fluid analysis, and (iii) all of the above and chest CT. We were able to make diagnosis in 53 patients (96%): the major cause of effusion was malignancy (38%). Clinical and biochemical data were not able to differentiate non-tumour from tumour patients. CT revealed pathological findings in all patients with malignancy: tumour mass in 15/21 (71%) and pathological lymphadenopathy in the remaining 6 cases. The workup including CT provided a significantly higher diagnostic yield than the other two workups ($P < 0.0001$), both in the overall population and in the two subgroups of neoplastic (Npl) and non-Npl patients.

Conclusion In all patients with cardiac tamponade or large pericardial effusion, CT was useful either in identifying the underlying disease or in excluding other potential causes of pericardial effusion. We conclude that chest CT is a very useful non-invasive diagnostic tool to identify and stage pericardial diseases.

Keywords Pericardial effusion • Cardiac tamponade • Echocardiography • Pericardium • Computed tomography

Introduction

Pericardial effusion may be caused by many disorders, such as infectious diseases, cancer, autoimmune, and metabolic diseases.[1–4] The underlying pathology is often known, but the diagnosis could be challenging for those patients who present with a pericardial effusion as the first sign of disease.[5,6] Clinical series of patients with large pericardial effusion have reported a low rate of idiopathic causes; conversely, a neoplastic (Npl) aetiology has been repeatedly and consistently reported and is associated with a poor prognosis.[7–10] An early diagnosis and treatment may favourably impact on the outcome of these patients.[11]

Among the imaging techniques used for diagnosis, echocardiography remains the cornerstone for its ease of execution and for

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its ability to assess the haemodynamic aspects of the effusion. Nevertheless, its diagnostic capability to recognize the underlying aetiology is low.[12]

In these patients, chest computed tomography (CT) can offer some advantages: this imaging technique allows assessment of the entire chest and detection of associated abnormalities in the mediastinum, lung, and adjacent structures.[12,13] The guidelines of the European Society of Cardiology for the diagnosis and management of pericardial diseases consider chest CT as an optional diagnostic tool that is indicated only when previous test results have been inconclusive.[2]

The aim of the present study is to evaluate the incremental value of chest CT in the aetiological investigations of patients with cardiac tamponade or large pericardial effusion as the first manifestation of the disease.

Methods

We had prospectively collected data from 123 consecutive patients, according to a predefined protocol, who underwent 141 echo-guided pericardiocentesis between 1993 and 2013: of these, 55 were included in this study based on the criteria depicted in *Figure 1*.

The indication for the pericardiocentesis was the presence of large pericardial effusion or cardiac tamponade. The effusion was classified as large if the sum of anterior and posterior echo-free spaces was major than 20 mm at end-diastole.[14] The diagnosis of cardiac tamponade was made with clinical parameters (tachycardia, dyspnoea, hypotension, and paradoxical pulse) and echocardiographic parameters (right ventricular diastolic collapse, right atrial collapse, and an inspiratory decrease in mitral E-wave velocity of 25% or more).[15–18]

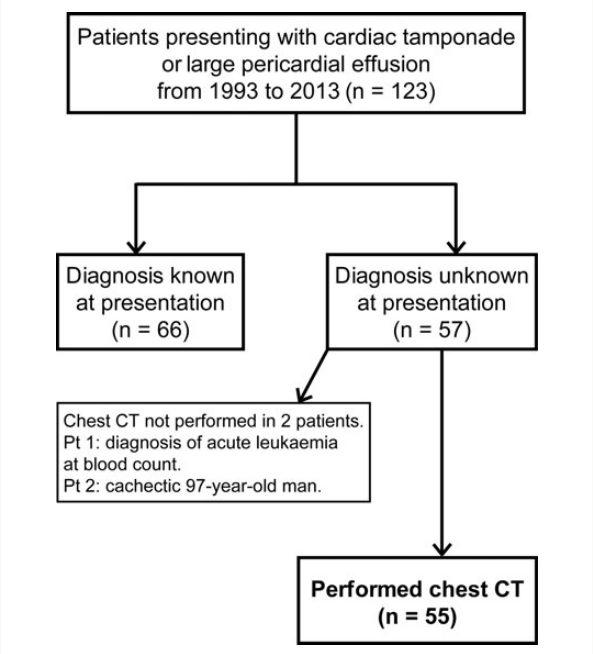

Figure 1 Flow chart of patient enrolment and selection criteria for the study.

Echo-guided pericardiocentesis was performed in the coronary care unit, using the bidimensional echocardiography to detect the position and amount of pericardial effusion. The percutaneous puncture was carried out in the site where the pericardial space was closest to the probe and where the largest amount of fluid was detected. The needle was advanced through the tissues and inside the pericardial space under continuous visualization according to the technique previously described.[19]

The 55 patients included in this study underwent the aetiological investigations recommended by the European Guidelines for the management of pericardial diseases and contrast-enhanced chest CT. Routine blood tests were performed, including C-reactive protein (CRP) and/or 'erythrocyte sedimentation rate' (ESR), LDH, and differential WBC. The pericardial fluid was tested for protein, LDH, and cholesterol levels; aerobic and anaerobic cultures; cytology; and culture and polymerase chain reaction to identify *Mycobacterium tuberculosis*. Other blood or instrumental tests were performed according to clinical conditions (such as anti-nuclear antibodies, thyroid function, liver function, etc.), if first-level tests were negative.

The diagnosis of viral or idiopathic acute pericarditis was assigned when the patient had a recent history of infection, elevation of inflammatory markers and clinical signs as typical chest pain, ECG modifications, self-limiting course of the disease, and when other causal factors could be excluded.[20] The diagnosis of chronic idiopathic pericardial effusion was made when the liquid persisted for at least 3 months without evidence of a specific cause. Effusion secondary to heart failure, end-stage renal disease, cirrhosis, and rheumatologic disease or associated with oral anticoagulant (OAC) therapy was diagnosed when these conditions were present in the absence of other specific causes.[5]

For each patient, we then compared the potential yield of three different workups to reach the final diagnosis/staging of the disease. The first workup included clinical presentation (fever, dyspnoea, chest pain, heart rate, and blood pressure), inflammatory markers (CRP, ESR, and WBC), and chest X-ray imaging (workup 1 = *w1*); the second included clinical presentation, inflammatory markers, chest X-ray, and pericardial fluid analysis (workup 2 = *w2*); finally, the third included all of the above analyses and contrast-enhanced chest CT scan (workup 3 = *w3*).

All patients gave permission for use of their clinical data for research purposes.

Statistical analysis

Continuous data are reported as mean ± SD and compared with two-tailed unpaired Student's *t*-test. Categorical variables are expressed as percentages and compared with the Fisher's exact test. The Cochran's *Q* test was used to compare the distributions of the two dichotomous outcomes (failure or success in diagnosing and/or staging the underlying disease) across the three workups, i.e. to analyse the success rate of the workups, followed by a *post hoc* comparison to assess which of the proportions are significantly different from which other proportions. A *P*-value of <0.05 was considered statistically significant.

Results

Fifty-five consecutive patients with pericardial effusion and/or cardiac tamponade of unknown aetiology at the presentation were identified. Patients' characteristics are reported in *Table 1*.

At the end of the aetiological investigation, we were able to make a final diagnosis in 53 of 55 patients (96%, *Table 2*), i.e. malignancy in 21 patients (38%), acute viral/idiopathic pericarditis in 10 cases (18%), bronchopneumonia in 6 cases (11%), associated with OAC therapy in 5 cases, tuberculosis in 4 patients (7%), autoimmune

Table 1 Baseline patient characteristics

	Cohort	Npl group	NNpl group	*P*-value
Patients, *n* (%)	55	21 (38.0)	34 (62.0)	
Sex, *n* (%)				
Male	34 (61.8)	14 (66.6)	20 (58.8)	0.776
Female	21 (38.2)	7 (33.4)	14 (41.2)	
Age (years)				
Mean ± SD (range)	62.2 ± 18.1 (16–92)	55.7 ± 18.0 (16–79)	66.2 ± 17.1 (32–92)	0.034
Clinical data, *n* (%)				
Fever	26 (47.3)	7 (33.4)	19 (55.8)	0.164
Dyspnoea	38 (69.1)	13 (61.9)	25 (73.5)	0.386
Chest pain	18 (32.7)	5 (23.8)	13 (38.2)	0.377
Tamponade	41 (74.5)	17 (80.9)	24 (70.5)	0.529
Biochemistry, *n* (%)				
Elevated CRP/ESR	46 (83.6)	17 (80.9)	29 (85.2)	0.719
Blood tumour markers	13 (23.6)	13 (61.9)	0	<0.0001
ECG, *n* (%)				
ST elevation	12 (21.8)	4 (19.0)	8 (23.5)	0.750
Low amplitude QRS	19 (34.5)	9 (42.8)	10 (29.4)	0.386
Chest X-ray, *n* (%)				
Pleural effusion	34 (61.8)	14 (66.7)	20 (58.8)	0.776
Parenchymal lung lesion	13 (23.6)	10 (47.6)	8 (23.5)	0.081
Pericardial fluid drained (mL)				
Mean ± SD (range)	862 ± 450 (120–2000)	886 ± 488	824 ± 392	0.626
Effusion's characteristics, *n* (%)				
Bloody	28 (50.9)	14 (66.7)	14 (41.2)	0.097
Serous	13 (23.6)	3 (14.3)	10 (29.4)	0.328
Serosanguineous	12 (21.8)	4 (19.0)	8 (23.5)	0.529
Purulent	1 (1.8)	0	1 (0.3)	1
Malignant cells in pericardial fluid, *n* (%)	11 (20.0)	11 (52.4)	0	<0.0001
Fluid LDH (UI/L)				
Mean ± SD	923 ± 834	1008 ± 920	871 ± 793	0.634

Npl, neoplastic; NNpl, non-neoplastic; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

disease in 2 patients (3.6%), uraemia in 2 patients (3.6%), as well as cholesterol pericarditis, anasarca in cirrhosis, and heart failure in 1 case each (1.8%). In the remaining two cases, the aetiological diagnosis remained unidentified. All diagnoses were confirmed at 6-month follow-up.

Comparison between Npl and non-Npl (NNpl) patients showed that clinical data (fever, dyspnoea, and chest pain) and biochemistry were similar, whereas mean age was significantly lower in Npl patients (*Table 1*, on the right). Chest radiography showed a parenchymal consolidation in 10 Npl patients, whereas in the NNpl group a pathological consolidation was found at the initial observation in 3 of 6 patients with pneumonia.

The volume of the pericardial fluid drained did not differ between the two groups. Excluding the 5 patients on warfarin, who belonged to the NNpl group in our series, bloody effusion was found in 14 of 21 Npl (66.7%) vs. only 9 of 28 NNpl patients (32.1%; $P = 0.022$). However, overall the sensitivity and specificity of bloody effusion to predict malignant pericardial disease were 66.7 and 58.8%, respectively. A positive result for cytological examination of the pericardial fluid was obtained in 11 of the 21 Npl patients (52.4%). In spite of its obvious very high specificity, the sensitivity of malignant pericardial effusion in predicting malignant disease was 52.4%.

Chest CT showed pathological findings in 29 of the 55 patients (52.7%), namely in all Npl patients and in 8 of the 34 NNpl patients (*Table 3*). A chest CT scan directly showed the tumour mass in 15 of 21 Npl patients (71%) and in the remaining 6 cases (29%) revealed pathological lymphadenopathy alone, defined as lymph nodes larger than 1 cm (*Figure 2*).[21–24] In patients with non-thoracic neoplasms (gastric, kidney, or genital cancer), a CT scan showed the renal mass or enlarged lymph nodes. Even in the case of tumour of unknown origin, CT revealed pathological lymphadenopathy. Detection of pathological adenopathies occurred in 13 of the 21 Npl patients (62%), but only in 3 of the 34 NNpl subjects (9%; $P < 0.001$): of these latter, one patient was affected by pneumonia associated with HIV, one by cholesterol pericarditis, and one by

tuberculosis. In all the four cancer cases with negative cytology and no bloody effusion, chest CT showed pathological findings: a mediastinal mass in the two patients with lymphoma, pathological lymph nodes in a patient with gastric cancer, and the renal mass in the case of kidney cancer. In patients without malignancy (*Figure 3*), chest CT demonstrated parenchymal lesions in all cases of pleuropericarditis associated with pneumonia and with non-diagnostic chest X-ray (three patients), and revealed pulmonary calcifications in two of the four patients with tuberculosis. Furthermore (*Figure 3*), chest CT excluded the presence of a tumour in all patients with bloody effusion either on OAC therapy or with acute pericarditis (five and four subjects, respectively) and in three patients with acute viral/idiopathic pericarditis without the classic presentation of a triad of fever, chest pain, and elevated inflammatory markers. Overall, the sensitivity and specificity of the presence of pathological nodules

Table 2 Aetiology of pericardial effusion

Aetiology	*n* (%)
Malignancy	21 (38.0)
Lung cancer	12
Lymphoma	3
Gastric adenocarcinoma	2
Cardiac sarcoma	1
Kidney cancer	1
Genital cancer	1
Metastatic primary tumour unidentified	1
Acute viral/idiopathic pericarditis	10 (18.0)
Associated with pneumonia	6 (11.0)
Associated with OAC therapy	5 (9.0)
Tuberculosis	4 (7.0)
Rheumatological disease	2 (3.6)
Uraemia	2 (3.6)
Heart failure	1 (1.8)
Cirrhosis	1 (1.8)
Cholesterol pericarditis	1 (1.8)
Chronic idiopathic	2 (3.6)

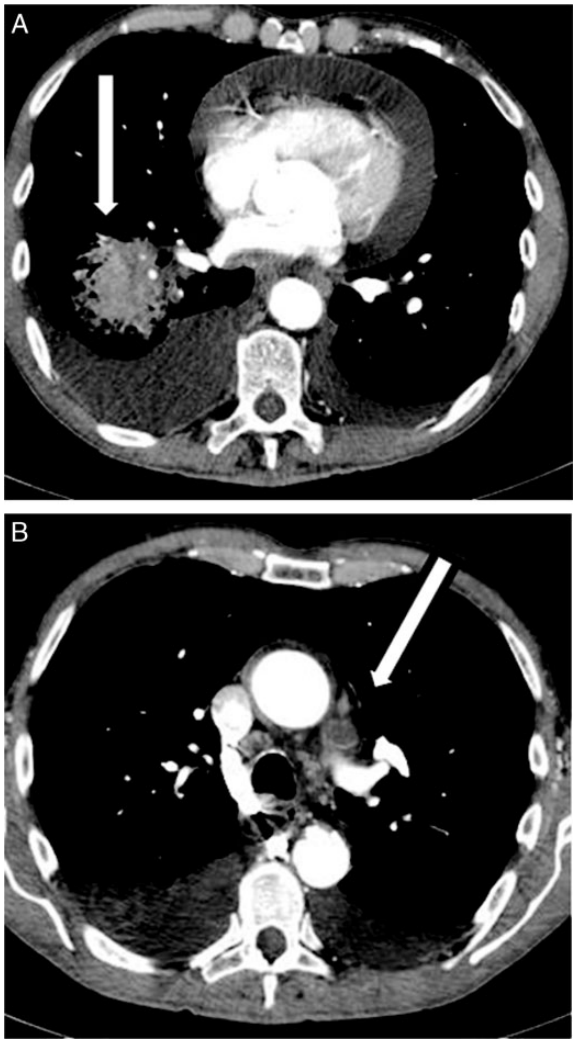

Figure 2 Representative chest CT scans with contrast enhancement, mediastinal window. (*A*) Lung cancer (white arrow), pericardial and pleural effusion. (*B*) Pathological mediastinal lymph node (white arrow).

Table 3 Chest CT results

Chest CT	NNpl	Npl	*P*-value
Number of patients	34	21	
Parenchymal lesions, *n* (%)	8 (23.5)	15 (71.4)	0.0007
Specific for pneumonia, *n* (%)	6 (17.6)		
Specific for tuberculosis, *n* (%)	2 (5.9)		
Pathological lymph nodes, *n* (%)	3 (8.0)	13 (61.9)	<0.0001
Calcified, strongly suspicious of tuberculosis, *n* (%)	1 (2.9)		
Aspecific[a], *n* (%)	2 (5.9)		
Negative, *n* (%)	26 (76.5)	0 (0)	<0.0001

Npl, neoplastic; NNpl, non-neoplastic.
[a]One associated with pneumonia in HIV infection, and one associated with cholesterol pericarditis.

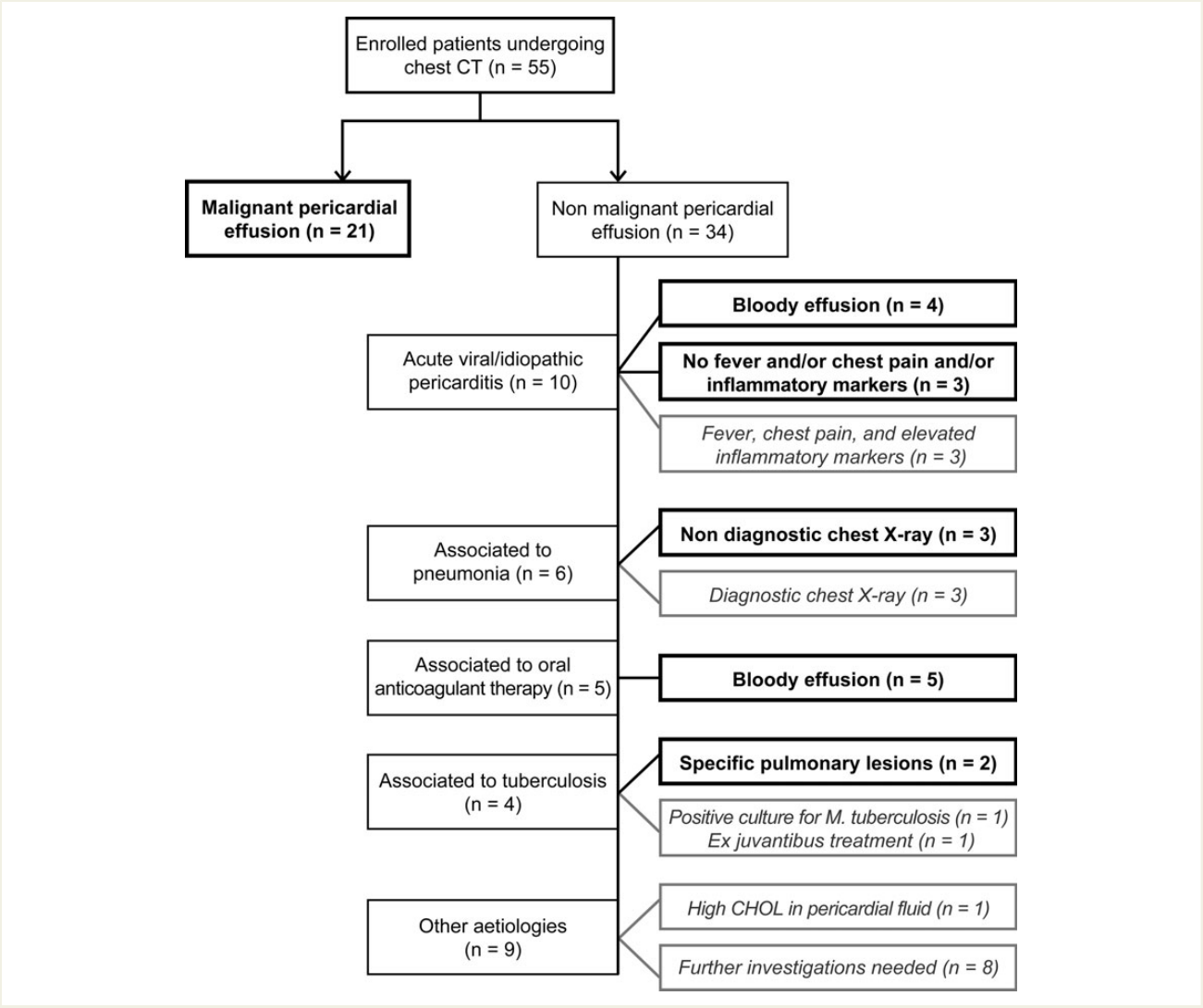

Figure 3 Chart showing the value of early chest CT scan in the diagnostic workup of patients presenting with cardiac tamponade or large pericardial effusion of unknown aetiology. Black boxes and bold text highlight cases with (on the left) or without (on the right) signs of malignancy, for which chest CT was essential in obtaining the final diagnosis. In patients with non-malignant conditions, chest CT (i) demonstrated inflammatory consolidations diagnostic for pneumonia undetectable to chest X-ray, (ii) showed pulmonary calcifications typical of tuberculosis, and (iii) ruled out the presence of a tumour in cases with bloody effusion or without fever and/or elevation in inflammatory markers. Grey boxes and italic text point out cases in which early chest CT was useful but not conclusive for differential diagnosis. In these cases, chest CT (i) confirmed inflammatory lung infiltrates in pneumonia detected by chest X-ray or (ii) excluded occult neoplasms.

and/or lymphadenopathies detected by chest CT in diagnosing malignant disease were 100 and 91.2%, respectively.

Finally, we compared the performance of the three different diagnostic workups described in the methods to reach a final diagnosis and/or definitive staging of the underlying disorder. As shown in *Figure 4A*, the yield of the workup that included CT scan (*w3*) was significantly higher when compared with *w1* and *w2*, which did not include CT scan (69.1, 10.9, and 25.5%, respectively). This was true also when we divided the total sample in the two subgroups of NNpl and Npl patients and compared the performance of the three workups within the two groups (*Figure 4B*): again, the workup including CT (*w3*) proved to be significantly better than *w1* and *w2*, both in the NNpl (50, 8.8, and 17.7%, respectively) and in the Npl group (100, 14.3, and 38.1%, respectively).

In eight patients, no workup was able to reach the final diagnosis (patients with cirrhosis, heart failure, uraemia, rheumatologic disease, or chronic idiopathic pericardial effusion) and further investigations were necessary. Still, chest CT was useful to exclude an occult neoplasm.

Discussion

The major finding of the present study was that for patients with cardiac tamponade or large pericardial effusion at presentation,

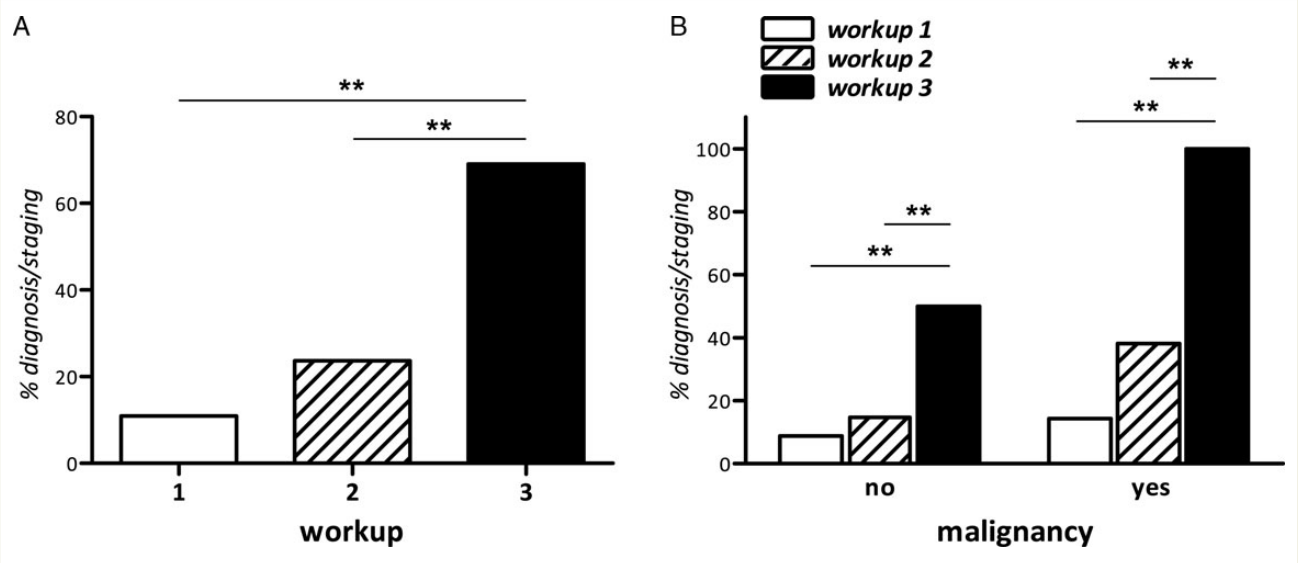

Figure 4 Yield of three workups in reaching final diagnosis/staging in patients presenting with cardiac tamponade or large pericardial effusion of unknown aetiology. Workup 1 included clinical presentation, inflammatory markers, and chest X-ray imaging; workup 2 included all of the above and pericardial fluid analysis; in workup 3, we added contrast-enhanced chest CT to workup 2. (*A*) Comparison of the performance of the three workups in the whole patient cohort. Significance of the Cochran's *Q* test: $P = 9.6 \times 10^{-9}$. (*B*) Comparison of the success rate of the three workups within the two subgroups of patients with or without malignancy. Significance of the Cochran's *Q* test: $P = 4.4 \times 10^{-6}$ and $P = 0.001$, respectively. $^{**}P < 0.01$, at *post hoc* pairwise comparisons.

the aetiology can be identified in most cases with a correct workup including early chest CT scan. In fact, only 3.6% of the effusions remained unclassified in our series. Malignancy was found in 38% of the patients and was the most common cause of pericardial disease. Similar observations are reported in other clinical series: Kabukcu *et al.*[25] and Cornily *et al.*[26] showed that cancer diseases were the most frequent cause of cardiac tamponade (30 and 65%, respectively). In our study, lung cancer was the predominant cause of malignant pericarditis, similar to other reports.[27–29]

Among the parameters usually employed in the diagnostic pathway, inflammatory markers and the amount of pericardial fluid were not able to differentiate patients with cancer, whereas the presence of bloody effusion was significantly higher in the group with malignant disease but with a limited sensitivity and specificity. The identification of malignant cells in the liquid was highly specific for cancer, but the sensitivity was rather low (52%). Similar data have been reported in the studies of Tsang *et al.*,[28] Pawlak Cieslik *et al.*,[29] and Maisch *et al.*[30] The use of invasive techniques, such as pericardial biopsy (not available in all centres), improves the diagnostic sensitivity, ranging from 24 to 85%, depending on the number of biopsies and the technique.[2,30] This procedure remains investigational and it is warranted only in skilled tertiary referral centres for selected cases, when a specific disorder is suspected and cannot be diagnosed by traditional diagnostic means.[6] The addition of chest CT, an easily available, non-invasive test, allowed making an aetiological diagnosis in 96% of our patients.

In the Npl group, chest CT revealed pathological findings in 100% of cases by direct visualization of the tumour (71%) and/or enlarged mediastinal lymph nodes (62%). No patient with malignancy had negative CT scan findings. The occurrence of pathological lymphadenopathies in patients with large pericardial effusion is an important marker of Npl disease, as documented by Sun *et al.*[31] and Pawlak Cieslik *et al.*[29] Sun *et al.* reported enlarged mediastinal lymph nodes in 60.7% of patients with malignancy and in 6.5% of patients without cancer, whereas Pawlak Cieslik *et al.* reported pathological findings in 90% of cancer vs. 29% of non-cancer patients. Notably, no patients with viral/idiopathic pericarditis had pathological lymphadenopathy (>1 cm) in our series.

Even in patients with negative cytology and non-haemorrhagic effusion, in which the probability of malignancy was low, chest CT allowed a definitive diagnosis, without further delay or use of invasive tests. Furthermore, in all patients with non-thoracic neoplasia, a CT scan detected abnormal findings: pathological lymph nodes in patients with gastric cancer, genital neoplasia, and cancer of unknown origin and a renal mass, being it adjacent to the diaphragm. These latter observations are important, because chest CT offers a clue to uncover non-lung Npl aetiology of the pericardial effusion.

In patients without cancer (*Figure 3*), early chest CT was essential for the aetiological diagnosis of pneumonia in cases without diagnostic X-ray (50% of the patients with this condition) and of pulmonary tuberculosis in cases with suspicious calcifications (50% of the subjects with this specific infectious disease). In addition, chest CT ruled out an Npl aetiology in 70% of patients with acute pericarditis (presenting either with bloody effusion or without the triad of elevated inflammatory markers, fever, and chest pain) and in 100% of patients on OAC therapy (all with bloody effusion). For patients with chronic

idiopathic pericardial effusion, cirrhosis, congestive heart failure, renal failure, or rheumatic disease, chest CT was instrumental for the final diagnosis by ruling out other possible causes. It should be emphasized that patients in our series did not suffer from a mild pericarditis and that those with known aetiology were excluded from the study. Conversely, these patients had all a severe pericardial effusion or cardiac tamponade of unknown aetiology at presentation, with no clinical features that allowed an *a priori* exclusion of cancer without performing chest CT (*Table 1*).

In assessing the added value of a workup that includes chest CT in comparison with two workups including tests recommended by the European Guidelines for the management of pericardial diseases, CT proved to be crucial in allowing us to reach a definitive aetiological diagnosis or to provide a strong suspicion which led to further appropriate investigations. It must be emphasized that in staging lung cancer patients, identified by positive cytology in the pericardial fluid, or in the cases of suspected neoplasia, pneumonia, and tuberculosis by chest X-ray, CT scan is part of the usual path and in our series, it allowed us to reach the diagnosis promptly.

All patients with cancer underwent a subsequent abdomen CT scan for disease staging, as suggested by the current guidelines. It could be argued about the opportunity to perform early chest and abdomen CT in one investigation, as this entails only a small increase in the radiation dose and a similar load of contrast media. Conversely, most of our patients without malignancy did not undergo an abdomen CT, because the final diagnosis was reached with the above-mentioned workups and was confirmed at 6-month follow-up. It therefore remains questionable whether performing early abdomen CT is useful in all patients with large pericardial effusion.

The aetiological diagnosis in patients presenting with tamponade or large pericardial effusion as the first manifestation of disease remains a challenge for the clinicians.[6,10] Several pathways have been proposed in which chest CT is not provided for a first-level diagnosis or it is regarded as a supplementary test, whether there is a strong suspicion of pulmonary disease or whether previous tests are inconclusive.[2,6] Our data suggest that in patients with cardiac tamponade or large pericardial effusion at presentation, a chest CT should be performed at the beginning of the workup together with the usual tests, taking into account its significant diagnostic capacity, non-invasiveness, and the large diffusion of the technique.

Conclusions

In our series, the prevalence of malignant disease in patients admitted for large pericardial effusion or cardiac tamponade as the first manifestation of the disease was high (38%). Clinical data (fever, dyspnoea, and chest pain) and biochemistry were not able to differentiate NNpl from Npl patients. Cytological examination of the pericardial fluid showed high specificity but low sensitivity in the diagnosis of Npl disease. In all patients with cardiac tamponade, chest CT was useful either in identifying the underlying disease or related signs or in excluding other potential causes of pericardial effusion. We conclude that chest CT is a very useful non-invasive diagnostic tool to identify and stage pericardial diseases.

Conflict of interest: none declared.

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IMAGE FOCUS

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An unusual cause of early aortic bioprosthetic valve failure

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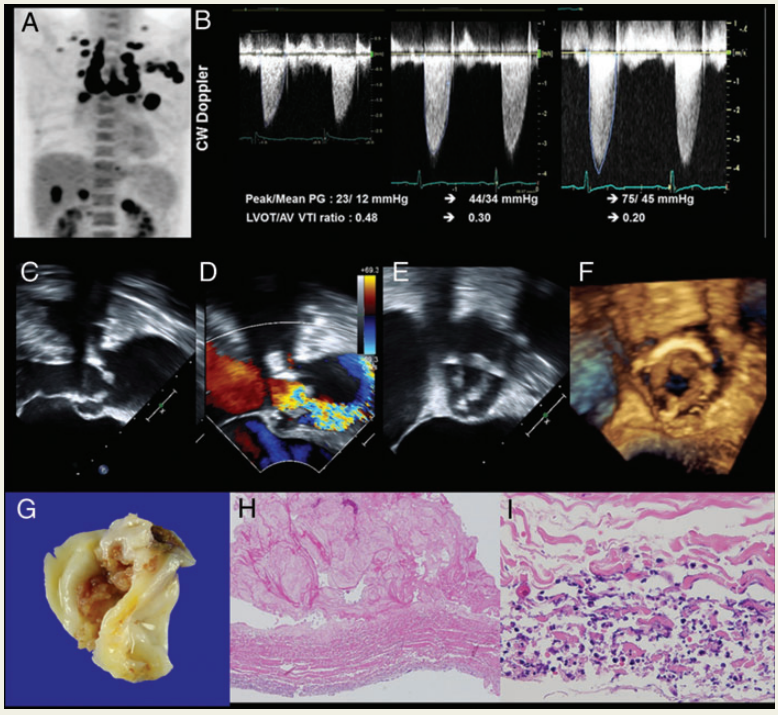

A 51-year-old woman was diagnosed with critical aortic stenosis due to a bicuspid aortic valve (AV) and metastatic lung adenocarcinoma with epidermal growth factor receptor (EGFR) mutation at the same time (*Panel A*). Two weeks after AV replacement with a 21-mm Carpentier-Edwards Perimount pericardial bioprosthesis (Edwards Lifesciences, Irvine, CA, USA), she started gefitinib (Iressa®) at 250 mg daily, a selective inhibitor of the EGFR signal transduction pathway. Although the gefinitib therapy showed a favourable response, she started having progressive chest pain and dyspnoea at 6 months after the surgery. Serial transthoracic echocardiography showed progressive increases of the maximum and mean pressure gradients across the bioprosthetic AV to 75 and 45 mmHg (*Panel B*). Transoesophageal echocardiography showed nodular thickening of the leaflets and consequent severe aortic stenosis and mild aortic regurgitation (*Panel C, D, E* and *F*; see Supplementary data online, *Video S1, S2, S3*). Serum inflammatory and rheumatologic markers were all negative. There was no evidence of bacterial or fungal endocarditis. Because her symptoms were not relieved, a redo AVR was performed using a mechanical prosthetic valve. The removed bioprosthetic AV revealed multiple nodular lesions and unusual degeneration (*Panel G*). Histologically, there were vegetative dense fibrinous material deposits on the valve and focal acute inflammatory cell infiltrations (*Panel H*). In the superficial layers of both sides of the valve, there were large numbers of macrophage deposits (*Panel I*). This case is the first to show a potential link between EGFR inhibition and AV inflammation and degeneration in humans, although it is highly evident in EGFR-deficient mice.

Supplementary data are available at *European Heart Journal – Cardiovascular Imaging* online.