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Pulmonary Embolism and Fever

When Should Right-Sided Infective Endocarditis Be Considered?

Gaetano Nucifora, MD; Luigi Badano, MD; Fjoralba Hysko, MD; Giuseppe Allocca, MD; Pasquale Gianfagna, MD; Paolo Fioretti, MD

Case presentation: A 39-year-old woman with chronic alcoholism became febrile (38.8°C) and markedly dyspneic on the fourth postoperative day of gastric surgery. Laboratory evaluation revealed anemia (hemoglobin 8.5 g/dL), thrombocytopenia (platelet count 30 000/mm³), and elevation of inflammatory markers (white blood cell count 18 000/mm³, C-reactive protein 187 mg/dL, and erythrocyte sedimentation rate 50 mm/s). Limb venous ultrasonography was negative for deep vein thrombosis, but pulmonary embolism (PE) was diagnosed on the basis of contrast-enhanced multidetector-row spiral computed tomography (MSCT; Figure 1A). Anticoagulation therapy was considered to be contraindicated because of recent surgery and thrombocytopenia, and a retrievable inferior vena cava filter was placed. With persistent high-grade fever and dyspnea and with the finding of *Streptococcus agalactiae* bacteremia, the patient underwent a transthoracic echocardiography examination on the sixth postoperative day that showed a large, mobile vegetation attached to the pulmonary valve (Figure 1B). A diagnosis of infective endocarditis (IE) of the pulmonary valve complicated by septic

PE was then made, and the patient was referred for vena cava filter removal and pulmonary valve replacement. During vena cava filter removal, an acute thromboembolic stroke occurred, and transesophageal echocardiography documented a patent foramen ovale with right-to-left shunt. Ten days later, the patient underwent successful pulmonary valve replacement and surgical closure of the patent foramen ovale.

Clinical Significance of Fever During PE

Fever has long been recognized as commonly accompanying PE. Stein et al¹ reported a temperature >37.5°C in 50% of patients with acute PE, but whether the fever was caused by the PE or an associated disease was not clarified. Murray et al² encountered fever >38°C attributed solely to acute PE in 57.1% of patients, whereas fever without any other definite or possible explanatory cause was observed in 14% of 311 patients in the PIOPED (Prospective Investigation Of Pulmonary Embolism Diagnosis) study.³ PE-related fever is usually low-grade, rarely exceeding 38.3°C, and short-lived, reaching its peak the same day

on which the PE occurs and gradually disappearing within 1 week.²⁻⁴

The pathogenesis of PE-related fever has not yet been fully clarified. It has been suggested that 1 or a combination of a variety of potential pyrogenic mechanisms occurs: infarction and tissue necrosis, hemorrhage, local vascular irritation or inflammation, atelectasis, or self-limited occult superinfections.^{2,5} The presence of a slight inflammatory response is indirectly confirmed by the concomitant increase of serum markers of inflammation.^{4,6} The presence of a modest leucocytosis (rarely exceeding 20 000/mm³) during the first hospital week is not uncommon, being described in up to 20% of patients with PE who have no other possible or defined cause of leucocytosis.^{2,7} The differential white blood cell count usually remains normal, only rarely showing a slight neutrophilia.⁷ Similarly, a slight increase in erythrocyte sedimentation rate and in C-reactive protein can also be observed.^{4,8}

True PE-related fever is not associated with the extension of vascular obstruction and does not have any prognostic role^{4,6}; its presence should not dissuade the clinician from diagnosing

From the Departments of Cardiopulmonary Science (G.N., L.B., G.A., P.G., P.F.) and Radiological Science (F.H.), Azienda Ospedaliero-Universitaria di Udine, Udine, Italy.

Reprint requests to Gaetano Nucifora, MD, Cardiopulmonary Science Department, Azienda Ospedaliero-Universitaria di Udine, P. le S. Maria della Misericordia 15, 33100 Udine, Italy. E-mail: gnucifora@cardionet.it

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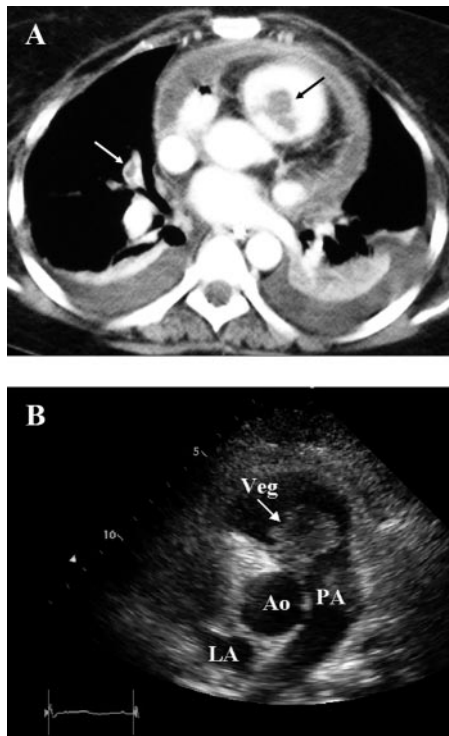


Figure 1. A, MSCT shows a large filling defect in the main pulmonary artery, above the pulmonary valve (black arrow), and a filling defect in the terminal part of the right pulmonary artery (white arrow). B, 2D transthoracic echocardiography performed a few days later shows a large vegetation attached to the arterial surface of the medial cusp of the pulmonary valve. Ao indicates ascending aorta; LA, left atrium; PA, pulmonary artery; and Veg, vegetation.

Diagnostic Role of Computed Tomography and Echocardiography

The introduction of MSCT has greatly improved the visualization of peripheral pulmonary arteries and detection of small emboli compared with spiral computed tomography (CT) angiography.^{12,13} Because of its better spatial resolution, MSCT is becoming the new standard of reference for imaging non-massive PE, and it is frequently used as the first-line imaging modality, alone or in combination with lung scintigraphy and inferior limb venous ultrasonography.^{12,13}

MSCT allows diagnosis of PE by disclosing vascular abnormalities (intravascular filling defects, total cutoff of vascular enhancement, or enlargement of an occluded vessel) and ancillary findings (pleura-based, wedge-shaped areas of increased attenuation with no contrast enhancement, linear atelectasis; Figure 3).¹² CT can also evaluate the presence of deep venous thrombosis in the abdomen, pelvis, thighs, and calves without additional intravenous injection of contrast mate-

PE and initiating appropriate therapy. Furthermore, PE-related fever usually subsides after anticoagulant treatment, whereas the addition of antibiotics does not provide any additional benefit.^{4,9}

The features of PE-related fever are similar to postoperative fever. Most early postoperative fevers (within the first 48 hours after surgery) have no clearly defined infectious cause and resolve without therapy. Therefore, among patients with onset of PE in the early postoperative period, fever could be also ascribed to the surgical procedure.¹⁰ Conversely, high-grade fever, especially if long-lasting or remittent and associated with a marked increase of serum markers of inflammation, could indicate advanced malignancy or pneumonia or other infections, or it could be the expression of septic embolic phenomena; it should prompt an exhaustive search for its cause, because management could be strongly affected (Figure 2; Table 1).^{2-4,6,11}

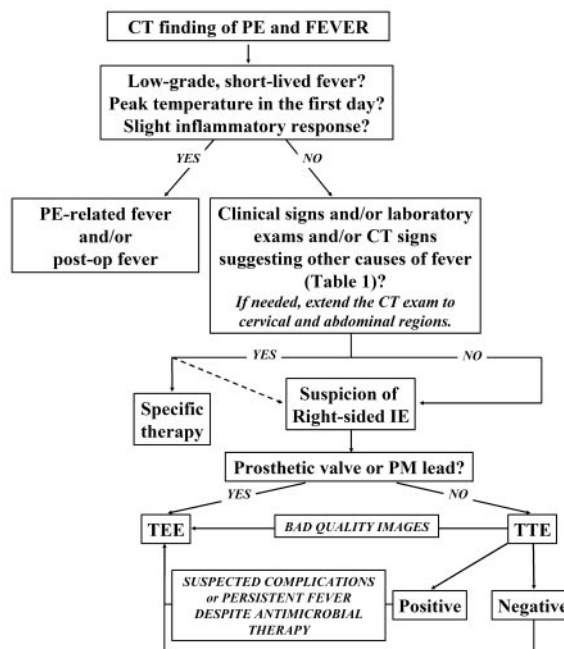


Figure 2. PE and fever: a clinical diagnostic algorithm. TEE indicates transesophageal echocardiography; TTE, transthoracic echocardiography; PM, pacemaker; and post-op, postoperative.

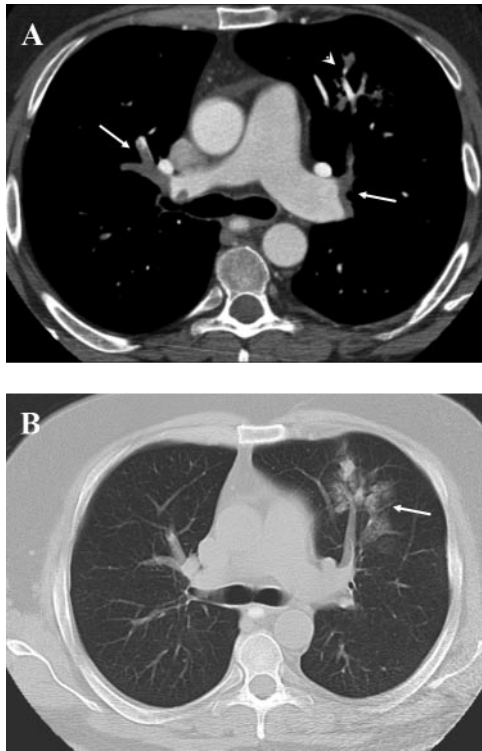


Figure 3. A, MSCT shows filling defects at the bifurcation of the left and right pulmonary arteries (white arrow) and multifocal filling defects in the segmental level of the left pulmonary artery (white arrowhead). B, MSCT (lung window) of the same patient shows focal peripheral confluent opacities in the anterior segment of the left upper lobe (white arrow), which suggests pulmonary infarction.

rial by scanning the lower limbs 3 to 4 minutes after scanning of the pulmonary vessels.¹²

However, among persistently high-grade febrile patients, the presence of

TABLE 1. Other Possible Causes of Fever Among Patients With PE

Cause	% of Cases
Advanced malignancy	33
Other infection with or without septic embolic phenomena	22
Recent operation	13
Trauma or multiple fractures	11
Pneumonia	9
Intracerebral bleed or acute stroke	4
Endotracheal tube	2
Delirium tremens	2
Polymyositis	2
Intraperitoneal catheter	2

Data derived from Stein et al.³

signs of PE should not deter one from searching for other potential causes of fever. The same CT examination can provide alternative explanations of fever (ie, thoracic or abdominal cancer, pneumonia or other infections) and is a valuable tool to identify septic PE phenomena.^{11,12} Characteristic CT findings in septic PE consist of discrete nodules with varying degrees of cavitation and subpleural, wedge-shaped heterogeneous areas of increased attenuation with rimlike peripheral enhancement. The nodules tend to be most numerous in the lower lobes. In many cases, a vessel can be seen leading directly to the nodules (“feeding vessel sign”).^{11,12} Unfortunately, these hallmark CT signs of septic PE are not always present (especially in case of fresh or large embolization), nor is the cause of PE always identifiable by CT (Table 2).¹⁴

Right-sided IE, a common cause of septic PE, is particularly difficult to

TABLE 2. Possible Causes of Septic PE

Lemierre syndrome (septic thrombophlebitis of the internal jugular vein secondary to acute oropharyngeal infection)
Right-sided IE
Infected central venous catheter
Dental abscess
Perinephric abscess
Osteomyelitis
Soft tissue infections

diagnose by CT because of the low temporal resolution of the technique, its inability to evaluate motion, and the presence of motion artifacts.¹⁵ Occasionally, some features, such as a filling defect inside the main pulmonary artery close to the pulmonary valve rather than the classic saddle embolus at the level of the bifurcation of pulmonary trunk, could suggest pulmonary IE (Figure 1). It is therefore crucial to maintain a high clinical suspicion of right-sided IE among patients with fever that is not justified by PE alone and without CT findings that potentially explain fever or septic PE phenomena, especially if the patient has risk factors for right-sided IE (ie, intravenous drug use, congenital heart defects, pacemaker leads, central venous lines, chronic alcoholism, dermal infections, malignancies, or immunologic deficiency).^{16,17} In this clinical scenario, transthoracic and transesophageal echocardiography should be performed without delay, even if not recommended by current guidelines on PE.^{18–20} Echocardiography has a strong diagnostic and prognostic role, with crucial therapeutic implications. Transthoracic echocardiography is generally adequate to correctly diagnose tricuspid vegetations.²¹ Transesophageal echocardiography should also be performed, because it is more sensitive in the diagnosis of pulmonary valve IE and pacemaker lead infections.^{22,23} Transesophageal echocardiography is also more valuable in recognizing prosthetic valve endocarditis and unusual locations of right-sided endocarditis (ie, the Eustachian valve) and in detecting IE complications (right-sided valvular insufficiency or dehis-

cence, congestive heart failure, and paravalvular abscesses).^{15,24,25}

In this group of patients, early implementation of echocardiography in the diagnostic algorithm alerts the clinician to appropriate antimicrobial therapy, which is usually sufficient to achieve remission of the infective disease without complications.¹¹ Persistent fever despite antimicrobial therapy, vegetations larger than 1 cm, multivalvular involvement, and right-sided heart failure identify patients at higher risk who may benefit from surgical treatment.^{16,26} Conversely, not performing echocardiography or performing it too late in these patients could expose them to potential complications that sometimes lead to death or significant morbidity, related not only to the progression of infection but also to an incorrect or even harmful treatment.

Conclusions

MSCT is frequently the first-line imaging modality in patients with suspected nonmassive PE. The use of echocardiography is limited to patients who are hemodynamically unstable and those with suspected massive PE; echocardiography may also be used to identify patients who could benefit from thrombolytic therapy.^{18,19} In the clinical scenario of documented nonmassive PE associated with unexplained persistent fever, early implementation of echocardiography could be of stronger diagnostic value, because right-sided IE could be the cause of septic PE. Its correct diagnosis can avoid potential complications related to inappropriate or even harmful treatment and to progression of infection, and it can address the appropriate antimicrobial (and eventually, surgical) therapy.

Disclosures

None.

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