Sonographic management of mediastinal syndrome

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KEYWORDS

Mediastinal syndrome;
Contrast enhanced US;
US-guided biopsy.

Abstract *Introduction:* Mediastinal syndrome is suspected on the basis of clinical symptoms and is generally confirmed by chest radiography or computed tomography (CT). However, also grey scale ultrasound (US) and contrast enhanced US (CEUS) are useful in this hematologic emergency as they provide the possibility to perform US-guided biopsy and histological diagnosis.

Materials and methods: 15 Patients affected by mediastinal syndrome were prospectively studied using B-mode US and CEUS; 13 of these patients, who had no other lesions, were proposed for US-guided biopsy of the mediastinal mass, but only in 12 patients biopsy was technically possible.

Results: In this study, B-mode US reached an excellent sensitivity (100%) in evidencing the lesions but a low specificity which did not exceed 30–40%. CEUS reached an elevated specificity identifying neoplastic pathologies if both the early and the late phases are considered (90–86.6%). US-guided biopsy was possible in 92.3% of lesions showing a diagnostic adequacy of 91.66%.

Conclusions: B-mode US associated with CEUS and US-guided biopsy reached an elevated accuracy in the diagnosis of mediastinal masses. If these results are confirmed by further studies, this diagnostic procedure could be included in the routine management of mediastinal syndrome.

Sommario *Introduzione:* La diagnosi di sindrome mediastinica viene sospettata dai sintomi e confermata da una radiografia standard del torace ed ancor meglio dalla TC, ma anche l'ecografia con e senza mezzo di contrasto (CEUS) può essere utile in questa emergenza ematologica, permettendo oltre tutto una diagnosi istologica tramite biopsia ecoguidata.

Materiali e metodi: 15 pazienti affetti da sindrome mediastinica sono stati prospetticamente studiati sia con l'ecografia B-Mode che utilizzando la CEUS. 13 di questi pazienti, senza altre lesioni sono stati proposti per una biopsia ecoguidata della massa mediastinica, che è stata tecnicamente possibile solo in 12.

Risultati: L'ecografia B-mode mostra in questo lavoro un'ottima sensibilità (100%), nell'evidenziare le lesioni, ma una bassa specificità che non supera il 30–40%. La CEUS mostra invece una buona specificità per le patologie neoplastiche se viene valutata sia la fase precoce che

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quella tardiva (90–86,6%). La biopsia ecoguidata è stata possibile nel 92,3%, mostrando un'adeguatezza diagnostica del 91,66%.

Conclusioni: L'ecografia B-Mode, associata all'ecografia con mdc ed alla biopsia ecoguidata delle masse mediastiniche, ha un'elevata accuratezza nella diagnosi delle masse mediastiniche, che se confermata da ulteriori lavori, può trovare indicazione nel management della sindrome mediastinica.

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Introduction

Mediastinal syndrome is a hematologic emergency characterized by dry cough, dyspnea and orthopnea, and it is often associated with edema involving face, neck and upper chest, swelling of the jejunal veins and other symptoms such as sweating, slightly elevated temperature, cutaneous and mucosal paleness and in some cases also itching. Chest radiography shows mediastinal enlargement, and the diagnosis is confirmed by computed tomography (CT) which evidences a mass in the anterosuperior mediastinum involving the thymic region and the large mediastinal vessels resulting in a more or less evident compression of the inferior vena cava and the anonymous veins, the trachea and more rarely the pericardium.

The most common expansive lesions occurring in the anterior mediastinum are thymomas, lymphomas, teratomas and masses originating from the thyroid. In the presence of mediastinal syndrome, it is important to exclude other reasons for lymph node involvement, particularly infectious conditions (tuberculosis, mycosis, and parasitosis), metastases, inflammatory granulomatous disorders (sarcoidosis and Castleman's disease) and immunological disorders (graft-versus-host disease and systemic lupus erythematosus), Still's disease, rheumatoid arthritis, etc. [1,2]. This requires a diagnosis confirmed by total body spiral CT and biopsy of possible neck lymph nodes, or CT-guided biopsy of the mediastinal mass if there are no neck lymph nodes. Ultrasound (US) examination of the mediastinum is an effective imaging method with an elevated sensitivity compared to traditional radiographic examination in patients with mediastinal masses, and it is only outperformed by CT in the examination of the posterior mediastinum and the paravertebral region [3–5]. Moreover, contrast enhanced US (CEUS) is proving increasingly useful in the differential diagnosis of lymph node masses [12,13], and US-guided mediastinal biopsy is a valid alternative to CT-guided mediastinal biopsy and even more to mediastinal biopsy carried out during mediastinoscopy [6].

Fifteen patients affected by mediastinal syndrome underwent prospective evaluation by B-mode US. Masses detected at US and confirmed by CEUS underwent US-guided biopsy.

Materials and methods

From January 2003 to June 2008, we examined 15 consecutive patients, 9 men and 6 women, mean age 44 years (range 18–69 years) who presented clinical signs of mediastinal syndrome characterized by dyspnea and orthopnea, cough, jejunal swelling, edema involving face and/or neck

and upper chest. All patients were HIV negative and had a clinical history negative for thoracic and/or extrapulmonary neoplasm. Ethical approval for this study was granted by the medical research ethics committee of our institution, and written informed consent was obtained from all patients.

All patients underwent chest radiography followed by B-mode US of the mediastinum, neck, armpits and abdomen. If mediastinal masses were evidenced at US examination, and no other pathological sites were located, CEUS and US-guided biopsy were performed. All patients were subsequently evaluated by CT or total body CT/positron emission tomography (PET).

Intracostal, supraclavicular and parasternal US scans evaluated presence of mediastinal lesions as well as size, bilateral location and US aspect using Tecnos MPX (Esaote, Genova, Italy) and a 3.5-MHz probe. Superficial pathological lymph nodes in the neck, armpits and groin were studied using a linear 10-MHz probe, whereas a 3.5-MHz probe was used in the study of deeply located abdominal lymph nodes.

During the same session, the mediastinal mass was studied by CEUS after intravenous bolus administration of 2.4 ml second generation sulphur hexafluoride contrast agent (SonoVue, Bracco, Milano, Italia) injected directly into the antecubital vein of the elbow and followed by 10 ml physiological solution. Contrast enhancement was evaluated in the early arterial phase (10–40 s) for presence, homogeneity, intensity and characteristics of the enhancement, and in the late parenchymal phase (40–120 s) for presence of enhancement and wash-out pattern.

After CEUS examination, patients who had no superficial enlarged lymph nodes underwent US-guided biopsy of the mediastinal mass using semi-automatic device BIOMOL (Hospital Service) and a 15-cm long 18 G needle. The patients were kept under clinical control after biopsy, and B-mode US examination and chest radiography were performed after 4 h.

Results

B-mode US of the mediastinum located bilateral lesions in 10 patients and monolateral lesions in 5 patients; mean dimension of the lesions was 6.3 cm in diameter (range: 4–8 cm). The lesions were characterized by large hypoechoic and/or inhomogeneous masses (Fig. 1a, Fig. 2a, Fig. 3a, and Fig. 4a), but only 2 patients had lymph nodes which appeared pathological at US: in the left supraclavicular region in one patient and in both armpits in the other.

In the early arterial phase, CEUS showed intense homogeneous enhancement in 5 patients, scattered

Fig. 1 (a) Left parasternal scan of the second intercostal space; an inhomogeneous mass is visible in the left anterosuperior mediastinum. S: sternum. (b) Left parasternal scan of the second intercostal space; 20 s after injection of 2.4 ml SonoVue there is intense, homogeneous enhancement of the mediastinal mass. (c) Left parasternal scan of the second intercostal space; wash-out occurs 45 s after injection of 2.4 ml SonoVue. (d) Left parasternal scan of the second intercostal space; US-guided biopsy of the mediastinal mass. Histological diagnosis: Hodgkin's lymphoma of mixed cellularity.

enhancement in 4 patients, poor peripheral ring enhancement in 3 patients, and intense but inhomogeneous enhancement due to avascular areas in 3 patients (Fig. 1b, Fig. 2b, Fig. 3b, and Fig. 4b).

In the late parenchymal phase, wash-out was observed within 60 s in 10 lesions and in 60–120 s in 4 lesions (Fig. 1c, Fig. 2c, Fig. 3c, and Fig. 4c) while enhancement persisted for more than 180 s in one patient.

Twelve patients who did not present superficial lymph node enlargement underwent US-guided biopsy of the mediastinal mass; right parasternal biopsy in 8 cases and left parasternal biopsy in 4 cases (Fig. 1d and Fig. 2d). In one patient who had a monolateral mediastinal lesion in the upper right region, US-guided biopsy was not possible as the lesion, which was partially visible at US, could not be reached by the needle due to the interposition of the ribs and the clavicle, and this patient therefore underwent CT-guided biopsy.

The 2 patients who had superficial lymph node enlargement underwent surgical biopsy the following day; one patient had a lymph node located in the supraclavicular region and the other patient had one in the right armpit.

Biopsy samples obtained under US guidance were adequate in 11/12 patients. Only one sample was inadequate and had to be repeated; however, as also the second sample was inadequate, biopsy was performed during mediastinoscopy.

Histological examination of samples obtained under US guidance showed Hodgkin's lymphoma in 5 patients (mixed cellularity: 2; nodular sclerosis: 2; lymphocytary depletion: 1). Non-Hodgkin's lymphoma was found in 4 patients (large-B-cell lymphoma: 3; T-cell lymphoma: 1). One patient had metastasis from pulmonary microcytoma and one had granulomatous disease suspicious for sarcoidosis.

Histological analysis in the 2 patients who underwent surgical biopsy yielded the following results: the lymph node located in the supraclavicular region was a metastasis of squamous cell carcinoma of the lung, and the lymph node located in the armpit was a Hodgkin's lymphoma (mainly lymphocytes).

Repeated biopsy performed at medianoscopy in one patient showed teratoma, whereas CT-guided biopsy performed in one patient showed pulmonary adenocarcinoma.

The patient who underwent biopsy of a supraclavicular lymph node (lymph node metastasis of squamous cell carcinoma of the lung) and the one who underwent CT-guided biopsy (pulmonary adenocarcinoma) presented poor peripheral ring enhancement at CEUS. This enhancement pattern was observed also in the patient who had microcytoma; in these 3 patients wash-out occurred in 60–120 s.

Six patients with Hodgkin's lymphoma presented the following enhancement pattern in the early phase: in 3 patients enhancement was intense and homogeneous, in 2 patients enhancement was scattered, and in one

Fig. 2 (a) Left parasternal scan of the third intercostal space; a large inhomogeneous mass is located in the left anterosuperior mediastinum. (b) Left parasternal scan of the third intercostal space; 29 s after injection of 2.4 ml SonoVue there is intense enhancement of the mediastinal mass; enhancement is inhomogeneous as the central area does not absorb contrast agent due to necrosis. (c) Left parasternal scan of the third intercostal space; wash-out of the mediastinal mass occurs 55 s after injection of SonoVue; the central avascular necrotic area is clearly depicted. (d) Left parasternal scan of the third intercostal space; US-guided biopsy of the mediastinal mass. Histological diagnosis: highly malignant non-Hodgkin's lymphoma.

patient enhancement was intense but inhomogeneous due to the presence of avascular areas. In 4 of these patients wash-out occurred within 60 s and in one patient wash-out occurred within 120 s.

Of the 4 patients who had non-Hodgkin's lymphoma, 2 presented scattered enhancement, while the other 2 presented intense, but inhomogeneous enhancement due to perfusion defects in the early arterial phase, but in all 4 patients wash-out was rapid and occurred within 60 s.

The patient who had a teratoma presented homogeneous enhancement in the early phase and wash-out within 60 s, whereas the patient who had a granulomatous pathology showed homogeneous enhancement in the early phase but wash-out within 120 s.

B-mode US permitted rapid identification of the lesion in all patients affected by mediastinal syndrome, reaching an elevated sensitivity but a poor specificity.

CEUS raised suspicion of malignant neoplastic pathology in the 3 cases of ring enhancement in the early phase, but due to the variability in imaging appearance of lymphomatous pathologies, the early phase was not specific even though there was intense enhancement in all cases of lymphoma, inhomogeneous in 30% and scattered in 40%.

In contrast, the late enhancement phase showed an elevated specificity as early wash-out occurred within 60 s in 90% of patients with lymphoma and within 120 s in 86.66% of patients with malignant neoplastic lesions. Enhancement pattern of teratoma was similar to that of neoplastic pathologies, whereas the granulomatous lesion presented a nonspecific enhancement in the early phase but a very late wash-out compared to neoplastic pathologies (later than 120 s).

In this study, US-guided biopsy was possible in 92.3% of cases (12 out of 13 patients) and was significant in 91.66% (11 out of 12 patients). None of the patients presented complications at US and radiographic follow-up, and only 3 patients (20%) complained of moderate pain at the biopsy site which disappeared within 15 min (Table 1).

Discussion

Mediastinal syndrome is characterized by a severe complex clinical picture of multiple etiologies which requires prompt diagnostic investigation in order to form a diagnosis and start adequate management as early as possible. At present, the diagnostic imaging method of choice is spiral

Fig. 3 (a) Left parasternal scan of the third intercostal space; a large inhomogeneous mass with a central hypoechoic area is located in the left anterosuperior mediastinum. (b) Left parasternal scan of the third intercostal space; 26 s after injection of SonoVue there is inhomogeneous enhancement with large irregular areas which do not absorb contrast agent due to necrotic avascular lesions. (c) Left parasternal scan of the third intercostal space; 50 s after injection of SonoVue, a rapid wash-out has eliminated all contrast agent. Histological diagnosis: highly malignant non-Hodgkin's lymphoma with large areas of necrosis.

CT which permits staging also of the abdomen and the skull in case of suspected neoplastic pathologies, even though PET/CT seems to reach a more elevated sensitivity and specificity in case of suspected pulmonary neoplasm and particularly in lymphomatous pathologies. Histological examination is performed on biopsy samples harvested from superficial lymph nodes, if any, or during fibro-bronchoscopy, CT-guided biopsy or mediastinoscopy. Lymphomas are the most common pathology in mediastinal syndrome. Hodgkin's disease can in fact originate in mediastinal lymph nodes, and in numerous cases mediastinal enlargement is incidentally observed if a chest radiography is taken in patients who present unspecific symptoms such as tiredness and increased heart rate [4,7]. Mediastinal involvement is often associated with superficial lymph node enlargement. Non-Hodgkin's lymphomas are less common than Hodgkin's lymphomas of the mediastinum, but at the time of diagnosis T-cell lymphoblastic lymphoma has generally involved the mediastinum with masses of considerable volume.

Lymph node metastases deriving from lung tumors are a less common cause of mediastinal syndrome, which is generally diagnosed when the neoplastic mass reaches a certain volume and/or is responsible for vascular

complications [8]. The diagnostic process is often long and this is a considerable disadvantage in patients who need to start radiation therapy and/or chemotherapy without delay.

B-mode US is rarely used in the study of the mediastinum, although this method is a valid diagnostic tool in addition to other techniques such as chest radiography, CT and MRI, as US of the mediastinum is much more sensitive than standard chest radiography in the diagnosis of mediastinal tumors.

Considering mediastinal CT as a reference method, US compared to radiography shows a higher sensitivity for each compartment: supraortic region 98% versus 67%, paratracheal region 89% versus 69%, aorta-pulmonary window 81% versus 62%, prevascular region 92% versus 46%, subcarinal region 69% versus 31%, and pericardial region 100% versus 67% [9].

Mediastinal US is less effective than CT in detecting supraortic, pericardic and perivascular lesions (sensitivity 98–100%) and some compartments such as the posterior mediastinal and paravertebral region can only be assessed by CT and MRI [10]. In lymph node pathologies CEUS shows a high accuracy in distinguishing benign from metastatic lesions as enhancement is intense and homogeneous in

Fig. 4 (a) Left and right parasternal scan of the second intercostal space; a mediastinal mass occupies the anterosuperior mediastinum on both sides. (b) Left parasternal scan of the second intercostal space; 37 s after injection of SonoVue there is scattered enhancement of the mediastinal mass. (c) Left parasternal scan of the second intercostal space; wash-out occurs 94 s after injection of SonoVue. Histological diagnosis: nodular sclerosing Hodgkin's lymphoma.

more than 90% of benign lesions, whereas enhancement is absent or poor in metastatic lesions [11,12]. Lymphomas present a variable enhancement pattern in the early arterial phase, often showing an overlap with both benign and metastatic lesions. The enhancement may be either intense and homogeneous, poor or scattered, and it is therefore useful to assess both the presence and characteristics of the arterial enhancement and the time and characteristics of the wash-out [11,13].

Successful outcome of a mediastinal biopsy depends on many factors including the clinical circumstances, site and size of the lesion, presence of comorbidity, operator experience and willingness of the institution to let this diagnostic method be performed. Percutaneous biopsy of the mediastinum is usually performed under US or CT guidance, as these methods provide accurate localization of the lesion and documentation of the biopsy sequence [14].

Alternative procedures are transbronchial biopsy performed during bronchoscopy with or without US guidance, biopsy performed during cervical mediastinoscopy and more rarely in the course of anterior mediastinotomy or thoracotomy. These procedures are used in order to reach areas inaccessible to standard mediastinoscopy.

The main limitation of transbronchial biopsy is the inability to visualize the lymph nodes and the needle during the procedure as well as the sensitivity of this method in the staging of pulmonary neoplasm ranging from 25% to 85%. It is therefore indicated mainly in patients with endobronchial lesions associated with mediastinal lymph node enlargement.

The advantage of echobronchoscopy is that a biopsy can be performed in real-time while the risk of pneumothorax is reduced and diagnostic accuracy is improved. Sensitivity reaches 82–96% although anterior, pretracheal and subcarinal lymph nodes located in the right upper lobe are not visible [15,16].

Table 1 Patient population with mediastinal syndrome evaluated using B-mode US, CEUS and US-guided biopsy.

Gender	Age	M/B	US	CEUS enhancement	CEUS wash-out seconds	Biopsy	Histology
Female	18	B	Hypo/In	Scattered	<60	US-guided	Non-Hodg
Female	27	M	Hypo	Intense homogeneous	<60	Surgical	Hodgkin
Male	52	M	In	Intense inhomogeneous	<60	US-guided	Non-Hodg
Male	44	B	Hypo/In	Intense homogeneous	<60	US-guided	Hodgkin
Male	61	M	Hypo	Ring	60–120	Surgical	Carcinoma
Female	34	B	Hypo/In	Scattered	60–120	US-guided	Hodgkin
Male	69	M	Hypo/In	Ring	60–120	CT-guided	Carcinoma
Female	58	B	Hypo	Ring	60–120	US-guided	Carcinoma
Female	19	B	In	Scattered	<60	US-guided	Non-Hodg
Male	24	B	Hypo/In	Intense homogeneous	<60	US-guided	Hodgkin
Male	44	M	In	Intense homogeneous	<60	US-guided (2) Mediastinoscopy	Teratoma
Female	39	B	Hypo/In	Intense inhomogeneous	<60	US-guided	Hodgkin
Male	47	M	Hypo	Scattered	<60	US-guided	Hodgkin
Male	59	B	Hypo/In	Intense inhomogeneous	<60	US-guided	Non-Hodg
Male	64	B	Hypo	Intense homogeneous	>120	US-guided	Sarcoidosis

Non-Hodg: non-Hodgkin's lymphoma; M: monolateral, B: bilateral, Hypo: hypoechoic; In: inhomogeneous.

Cervical mediastinoscopy is considered the gold standard in the staging of non-small cell lung tumors as it permits a direct assessment and sampling of pretracheal, paratracheal and anterior subcarinal lymph nodes with the possibility of diagnosis in 83–89%. However, this procedure requires general anesthesia and is associated with complications in 1–3% of cases.

US- or CT-guided biopsy is possible in nearly all mediastinal regions providing a correct diagnosis in 75–90% of cases, although particularly CT-guided transthoracic biopsy presents a high rate of pneumothorax varying from 10% to 60%.

Complication rates of US-guided biopsy are particularly low and diagnostic accuracy is elevated, as this method is able to locate the lesion and identify a safe path for the positioning of the needle. Generally convex 3.5–7.5 MHz probes are used depending on the thickness of the soft tissue and the distance between the lesion and the skin. Before the procedure is carried out, color Doppler is performed to locate large vessels [17].

Numerous institutions perform needle aspiration biopsy using fine needles (FNAB) which permit aspiration of material for cytological analysis, but also needles with stylet of a calibre ranging from 14 G to 22 G are used as they permit sampling of tissue.

FNAB of mediastinal metastatic lesions originating in epithelial tumors reaches a sensitivity of 84–100%, but biopsy using needle with stylet should be the method of choice in lesions suspicious for lymphoma, since the sensitivity of FNAB in lymphomas varies from 42% to 82%, whereas the procedure carried out using needles with stylet provides a correct diagnosis in 91% of cases. The use of automated needles has improved diagnostic yield without increasing complication rates.

After US-guided mediastinal biopsy, patients are kept under observation for 1–3 h for assessment of hemodynamic stability and respiratory status; 3–4 h after the procedure, a chest radiograph is taken during exhalation, and US of the mediastinum is performed to exclude pneumothorax and/or pneumomediastinum [18–20].

The experience reported by the authors shows an elevated sensitivity of B-mode US in identifying the lesions in all cases of mediastinal syndrome and in allowing the identification of pathological lymph nodes in adjacent sites such as the neck and the armpits.

CEUS may prove useful also in the diagnosis of malignant lesions of the mediastinum showing a variable enhancement pattern in the early stage, although scattered enhancement appears only in lymphomatous lymph nodes. Particularly wash-out is very quick in this disease. The few cases of pulmonary neoplasm examined in this study were characterized by poor vascularization in the early stage while wash-out occurred later than in lymphoma. In neoplastic pathologies, contrast enhancement frequently evidences areas of necrosis characterized by avascular areas already in the early arterial phase. In this study, US-guided biopsy provided a correct diagnosis without complications.

The benefits of US-guided biopsy include diagnosis in real-time, the possibility to continuously monitor the needle during sampling and to follow an oblique needle path while avoiding areas of necrosis identified at CEUS. Biopsy can be carried out with the patient in bed, also critically ill patients affected by dyspnea, and it can be performed in partial sit-up position in patients who do not tolerate the supine position, as it often happens in patients affected by mediastinal syndrome. Without incurring complications, this diagnostic procedure provides the possibility to suspect or rule out malignant neoplastic disease and to obtain a prompt histological confirmation in almost all cases in order to start appropriate therapy.

Conclusions

A correct and fast management of mediastinal syndrome including B-mode US, CEUS and US-guided biopsy, if required, provides rapid identification of lesions and the possibility to evaluate the malignancy of the pathology, permitting prompt appropriate treatment of this onco-hematologic emergency.

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