

Cytology on Transbronchial Needle Aspiration (TBNA): Not Only for Lung Cancer

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Abstract. *Transbronchial needle aspiration (TBNA) is a bronchoscopic technique allowing the sampling of cytological/histological material from mediastinal lymph nodes. TBNA is routinely used only in few centers for the staging of lung cancer, and even less frequently for the diagnosis of mediastinal metastases from extrapulmonary tumors. We illustrate 5 cases of mediastinal metastases from extrapulmonary tumors observed at our center in order to emphasize the usefulness of cytology and TBNA in the diagnosis of these pathologies. The 5 cases illustrated were: seminoma, uterine cervical carcinoma, pleural mesothelioma, pancreatic carcinoma, pericardial mesothelioma. In these 5 cases, albeit not of lung cancer, the cytology on TBNA allowed the rapid formulation of the correct diagnosis; its main advantage is that it can be performed during a simple fiberbronchoscopy under local anesthesia with less risk and at a lower cost than a computed tomography- guided needle biopsy or mediastinoscopy.*

Transbronchial needle aspiration (TBNA) is a bronchoscopic technique allowing the sampling of cytological/histological material from mediastinal lymph nodes. It is mainly used for the diagnosis and staging of lung cancer (1). For this technique to be successfully implemented, a few requirements must be fulfilled: the lymph node must be in contact with the walls of the airways and the pneumologist performing the technique and the cytologist reading the results require specific training (2, 3).

The factors impacting on TBNA sensitivity are: presence of computed tomography (CT)-revealed lymphadenopathies, operator skill and experience, type of needle

used, lymph node localization and diameter, number of aspirations performed, rapid on site examination (ROSE), nature of the lesion (lung cancer, metastases from other neoplasms, sarcoidosis, tuberculosis, etc.) and use of guiding techniques (3-9). Technique sensitivity ranges between 70 and 85% on account of the aforementioned factors, or more if performed by an experienced operator, or if endobronchial ultrasound-guided; specificity ranges between 96% and 100%. TBNA is routinely used only in few centers for the staging of lung cancer, and even less frequently for the diagnosis of mediastinal metastases from extrapulmonary tumors (8, 10-14).

This paper illustrates 5 cases of mediastinal metastases from extrapulmonary tumors observed at the host center between January 2008 through 2009, in order to emphasize the usefulness of cytology and TBNA in the diagnosis of these pathologies.

All TBNAs were carried out in the course of the first fiberbronchoscopy performed on the patients at the host center. A total of 60 patients were included in the study. The final diagnosis was formulated based on the results of a morphologic cytological examination and of immunocytochemistry or molecular biology techniques, where deemed necessary by the cytologist.

In 78% of cases (47/60), cytology on TBNA allowed a definite diagnosis. In particular 30 non-small cell lung cancer cases (nine squamous carcinomas, sixteen adenocarcinomas, five large cell carcinomas), five small cell lung cancer cases, five neuroendocrine large cell lung tumors, two sarcoidoses, five metastases from extrapulmonary tumors. In 13 cases that had remained undiagnosed after TBNA, the patients were subjected to mediastinoscopy, which revealed ten lymphomas and three sarcoidoses. This TBNA case survey had a positive predictive value of 1 and 78% accuracy.

Lymph node metastases from extrapulmonary tumors accounted for 9% of all neoplasia diagnoses in this study. Hereinafter five cases are illustrated: seminoma, uterine cervical carcinoma, pleural mesothelioma, pancreatic carcinoma, pericardial mesothelioma.

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Case Reports

Case 1. Male, 35-year-old 15 pack year (p.y.) smoker; mother died at 56 of small cell lung cancer, one 33-year-old brother with acute myeloid leukemia. In November 2004, the patient, having been diagnosed with a pure seminoma (immunohistochemical analysis positive for placental alkaline phosphatase (PLAP) and periodic acid schiff (PAS), negative for cytokeratin (CK)), underwent right orchiectomy/funiculectomy (pT1, Nx, M0, stage I). In February 2005, the patient underwent radiotherapy (25 Gy) to both lumboaortic lymph nodes. The patient was negative for lymph node enlargement and metastasis on CT scan during the follow-up until March 2008, when a CT total body scan revealed a mediastinal mass. The patient was then subjected to TBNA of the anterior carenal lymph node with a 21 G needle (Olympus Europa GmbH, Hamburg, Germany). The morphological examination showed monomorphic population of dispersed neoplastic cells resembling blast cells, the immunocytochemistry PLAP⁺, thyroid transcription factor 1 (TTF1)⁻, CK⁻ and cytochemistry (PAS⁺) analysis suggested a diagnosis of lymph node metastasis originating from a seminoma (Figure 1).

The patient's β -HCG was 16.6 mUI/ml and α -fetal protein 1.09 IU/ml. In April 2008, the patient started chemotherapy with platin, epirubicin and bleomycin; the patient underwent six chemotherapy cycles. In November 2008, total body PET did not show any tracer distribution anomalies; α -fetal protein 1.5 IU/ml, β -HCG 0 mUI/ml. The patient's follow-up at the time of writing included blood tests and CT; in April 2009, the patient's CT confirmed a persistent absence of disease.

Case 2. Female, 37 years old, in May 2007 underwent a radical hysterectomy according to Piver III, bilateral salpingectomy and bilateral pelvic lymphadenectomy for invasive cervical uterine squamous carcinoma. The postoperative histological examination did not show any residual neoplasia: the right and left parametrium, the vaginal resection margin and the salpinx appeared free from neoplastic infiltration; the 15 removed lymph nodes were free from metastases. From October 2007, follow-up was negative for disease recurrence.

In February 2009, the patient started complaining of epigastralgia and dysphagia after both solid and liquid intake, dry cough, vomiting, and lost 8 kg in three weeks. A chest CT examination (Figure 2) showed a 4 cm neoformation with dyshomogeneous contrast medium uptake in the third esophageal medium section. The lesion caused tight stenosis of the esophagus with dilatation of the upper proximal tract; 20 mm lymph nodes partially enclosed in the seat of the lumbar aorta. A TBNA of the retroarenal lymph node was then performed using a 19 G MWF 319 needle

(ConMed Italia, Milan, Italy). ROSE was performed and the cytologist requested further samples for more analysis.

The morphological examination showed cells in syncytia, cytoplasm was cyanophilic with prominent nuclear irregularities (Figure 3). The immunocytochemistry (TTF1⁻) and qualitative reverse dot blot PCR (human papilloma virus HPV31⁺) revealed a metastasis from uterine cervical carcinoma. The same viral type was previously detected in the primary tumor after hysterectomy and histological examination.

In early March 2009, the patient began cisplatin and vinorelbine chemotherapy and, at the end of the month, received an esophageal stent. In May 2009, a chest CT showed the esophageal stent as well as an unchanged radiological picture of the retrotracheal neoplasia.

At the time of writing, the patient was in good general conditions and continues her chemotherapy treatment.

Case 3. Male, 70 years old, (ceased smoking a month before, 30 p.y.), construction worker, was hospitalized in the Pneumology Department in January 2008 due to ingravescent dyspnea. A CT of the chest showed left pleural effusion and thickened pleura, as well as a small pleural implant area in the costodiaphragmatic excavation; 1 cm left and right paratracheal lymphadenopathies, a 3 cm subcarinal lymph node and left and right hilar lymphadenopathies of approximately 2 cm.

A TBNA of the subcarinal lymph node was performed using a 21 G (Olympus Europa GmbH) needle.

The morphological examination showed depicting neoplastic tissue fragments, further immunocytochemistry analysis (calretinin⁺, CK5/6⁺, TTF1⁻) revealed malignant mesothelioma of the epithelial type conclusive for a diagnosis of multiple lymph node metastases from pleural mesothelioma (Figure 4).

The patient was subjected to pleuroscopy with pleural biopsy which confirmed the diagnosis of mesothelioma. In February 2008, the patient began chemotherapy with carboplatin and pemetrexed. After three chemotherapy cycles, the patient's general condition gradually worsened and, in agreement with the patient, treatment was suspended; the patient died in July 2008.

Case 4. Male, 44 years old, was subjected to distal pancreatectomy and splenectomy for a ductal pancreatic adenocarcinoma (T3, N1, Mx, G3, stage II B) in May 2008. In consideration of the stage of the disease, surgery was followed by radiotherapy and chemotherapy.

In April 2009, after three treatment cycles, a total body CT scan showed a left hilar neoformation at chest level of approximately 3 cm. For this reason the patient was subjected to fibrobronchoscopy with TBNA performed with a 21 G (Olympus Europa GmbH) needle and ROSE showed presence of neoplastic cells.

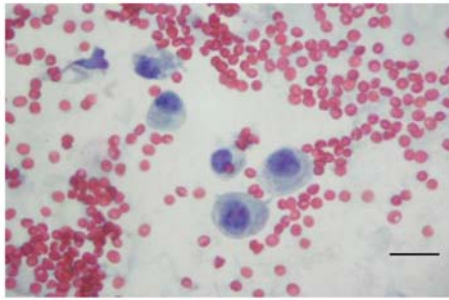


Figure 1. Monomorphic population of dispersed neoplastic cells resembling blast cells (bar: 25 μ m).

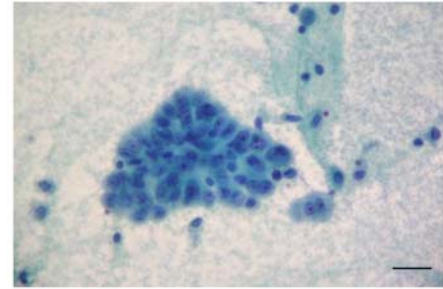


Figure 4. Smear of TBNA depicting tissue fragments of diffuse malignant mesothelioma of the epithelial type (bar: 25 μ m).



Figure 2. Chest CT scan of retrocarinal lymph node enlargement.

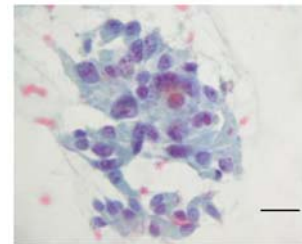


Figure 5. Well-differentiated ductal adenocarcinoma of the pancreas. Aggregates of malignant cells with coarse chromatin and variations in nuclear size and shape (bar: 25 μ m).

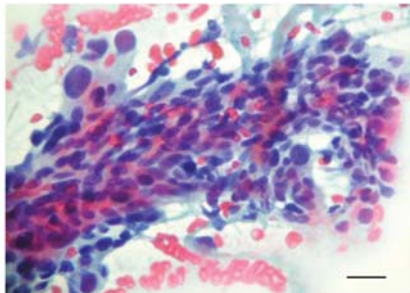


Figure 3. Cells are in syncytia. Cytoplasm is cyanophilic with prominent nuclear irregularities (bar: 25 μ m).

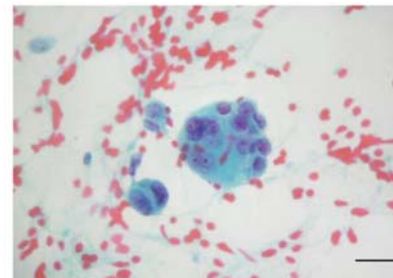


Figure 6. Large clusters with round nuclei, prominent nucleoli, and dense cytoplasm with a pale rim (bar: 25 μ m).

The morphological examination showed aggregates of malignant cells with coarse chromatin and variations in nuclear size and shape (Figure 5). The immunocytochemistry (TTF1⁻, CK7⁺) with clinical data and radiological pattern yielded a diagnosis of metastasis from adenocarcinoma of the pancreas.

At the time of writing, the patient was undergoing treatment with taxotere and was in good general condition.

Case 5. Male, 49 years old, with nothing relevant in his medical history. The patient was admitted to the emergency room of the hospital with a stabbing pain in the right side of the chest. Pain decreased after paracetamol administration. The patient was subjected to several diagnostic procedures including chest X-rays and CT which showed the presence of pleural effusion, heart tamponade and mediastinal lymphadenopathy. The patient was subjected to thoracentesis; the analysis of the fluid was negative for bacteria and neoplastic cells. The patient was then subjected to fibrobronchoscopy with TBNA of the lymph node situated anteriorly to the main left bronchial tube. The morphological examination of the sampled material showed large clusters with

round nuclei, prominent nucleoli, and dense cytoplasm with a pale rim, the immunocytochemistry analysis (TTF1⁺, caudal type homeobox transcription factor 2-negative, Hectort Battifora mesothelial cell 1-positive, mesotelin-positive) suggested a diagnosis of metastasis from pericardial mesothelioma (Figure 6). The patient was subjected to pericardiocentesis which was positive for neoplastic cells. At the time of writing, the patient was undergoing chemotherapy.

Conclusion

TBNA is a technique used to obtain samples from mediastinal lymph nodes. It is a technique underused by pneumologists and oncologists alike (14). The main case surveys reported in the literature focus on the sensitivity and specificity of the method, especially in the diagnosis of lung cancer (15-17); in the above mentioned cases, albeit not of lung cancer, the technique allowed the rapid formulation of the correct diagnosis which allowed treatment to begin within a short time. Its main advantage is that it can be performed during a simple fibrobronchoscopy under local anesthesia with less risk and at a lower cost than a CT-guided lung needle biopsy or mediastinoscopy. As far as the nature of the diagnosed lymphadenopathies is concerned, usually, if there is a suspicion of non-pulmonary metastases, it is preferable to use a 19 G needle with mandrel in order to obtain a biopsy sample for histological examination (5-8). The reported cases were diagnosed based on the results of the cytological examination and of the immunocytochemical analysis; in the case of the pleural mesothelioma, the diagnosis was confirmed by the histological evidence of the pleural biopsies. This shows that in certain situations, especially in cases of suspected metastases from a tumor that has been previously biotically characterized, it is sufficient to obtain samples for the cytological analysis, particularly if it possible to carry out a ROSE as in case 2 and 4. The rapid on-site analysis of transbronchial aspirates is a highly useful, accurate and cost-effective addition to routine diagnostic bronchoscopy (18). The Authors' experience revealed that ROSE is useful not only for the pneumologist but also for the cytologist in order to obtain adjunctive samples for ancillary analysis such as molecular biology and immunocytochemistry.

The reported cases show that the pneumologist and the oncologist should have a knowledge of TBNA with rapid on-site examination and consider it a primary diagnostic option in cases of suspicion of mediastinal lymphadenopathies due to metastases from extrapulmonary tumors.

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