

Tracheobronchial puncture-site nodular reaction (TPNR) following endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA): Systematic review of case reports

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ABSTRACT

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a minimally invasive and efficacious diagnostic modality for lung cancer staging and evaluation of undiagnosed mediastinal lymphadenopathy. Procedure-related complications are uncommon. We herein report an infrequently described phenomenon following EBUS-TBNA in which two patients developed nodular granulation tissue at the tracheobronchial puncture site. On systematic review, we found description of such phenomena by terminologies such as endobronchial inflammatory polyp, granuloma, and endobronchial mass. The endobronchial inflammatory polyp has been one of the most commonly used terminologies for these; but in most cases, the classical features of an inflammatory polyp are lacking. We propose the term, tracheobronchial puncture-site nodular reaction (TPNR) with further classification into granulomatous and nongranulomatous subtypes, for standardized reporting of such reactions following transbronchial needle aspiration procedures. Knowledge of this entity and standardized nomenclature shall help in better characterization of the outcomes and risk factors for the occurrence of these reactions.

KEY WORDS: Bronchoscopy, endobronchial ultrasound, transbronchial needle aspiration

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INTRODUCTION

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a firmly established modality for evaluation of undiagnosed mediastinal lymphadenopathy due to various etiologies including lung cancer and granulomatous mediastinal lymphadenopathy.^[1] The horizon of this technique is gradually expanding with increasing global adoption and newer performance indications.^[2,3] Although a number of procedure-related complications are described, the overall complication risk is minimal.^[4]

Few reports have described the development of reactions at the puncture site following EBUS-TBNA. As

EBUS-TBNA essentially involves a needle puncture of the tracheobronchial wall, puncture site reactions may occur. Instead of a standardized nomenclature, these have been described by various terminologies such as endobronchial inflammatory polyp, endotracheal granuloma, and endobronchial mass formation.^[5-9] Lack of a standardized terminology and rarity of description of such entities may be responsible for underreporting of these reactions. We perform a systematic review of the available literature on these entities, and subsequently propose a term, tracheobronchial puncture-site nodular reaction (TPNR) for these benign reactions that develop

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subsequent to EBUS-TBNA. We also report two patients who developed a TPNR following EBUS-TBNA.

CASE REPORTS

Case 1

A 53-year-old male presented with a history of gradual onset painful loss of vision and was diagnosed as bilateral anterior uveitis. Contrast-enhanced computed tomography (CT) scan of the thorax showed multiple enlarged homogenous appearing mediastinal lymph nodes (LNs) predominantly at the lower right paratracheal and subcarinal stations [Figure 1a]; a possibility of granulomatous etiology (tuberculosis [TB] vs. sarcoidosis) was considered. The patient was a lifetime never smoker and was diagnosed with diabetes mellitus and systemic hypertension that were controlled with medications. Tuberculin skin test showed induration of 14 mm while serum angiotensin converting enzyme levels were normal. EBUS-TBNA was performed using Olympus BF-UC-180-F EBUS bronchoscope (Olympus Corporation, Japan) from the lower right paratracheal (Station 4R) and subcarinal LN stations (Station 7) using a 21-gauge aspiration needle. Three passes each were performed from each of the stations, and there were no procedural complications. Cytological analysis of the aspirates demonstrated adequate lymphoid tissue, but no definitive pathology was evident.

In view of a strong possibility of mediastinal TB, repeat EBUS-TBNA was performed 2 weeks later. On scope introduction and airway inspection, a nodular whitish lesion was found in the lower right lateral tracheal

wall (at the site of right paratracheal LN TBNA puncture site [Figure 1b]). Biopsy from the endotracheal nodule revealed focal ulceration, acute inflammatory exudates, and granulation tissue [Figure 2]. No granulomas were identified. Cytological analysis of EBUS-TBNA aspirates from subcarinal LN demonstrated granulomas with necrosis; the patient was initiated on antitubercular therapy. On follow-up bronchoscopy performed 2 months later, the nodule had resolved.

Case 2

A 53-year-old female reformed smoker was diagnosed as a case of possible paraneoplastic limbic encephalitis (serum anti-Hu antibody positive), and an FDG (fluorodeoxyglucose)-PET (positron emission tomography)-CT scan was performed for further evaluation. PET-CT demonstrated FDG avid left lower lobe lung nodules along with FDG avid paratracheal and subcarinal LNs [Figure 1c] and was referred for EBUS-TBNA. EBUS-TBNA was performed from the subcarinal and bilateral lower paratracheal LN stations using the 21-gauge EBUS-TBNA needle. Cytopathological examination of the EBUS-TBNA aspirates demonstrated crush artifacts and no definite opinion was possible. Two weeks later, repeat EBUS was performed. An endobronchial nodule was seen in the proximal right main bronchus at the subcarinal location at the site of previous EBUS-TBNA needle puncture [Figure 1d]. Endobronchial biopsy was obtained from the nodule, and histopathological examination demonstrated granulation tissue without any evidence of granuloma or malignancy. Repeat EBUS-TBNA from lower right paratracheal station confirmed a diagnosis of small cell carcinoma. The patient was initiated on chemotherapy with cisplatin and etoposide. The patient was subsequently lost to follow-up.

Systematic review

We performed a systematic search of the PubMed and Embase databases (for years 2004–2015) to identify the studies reporting the occurrence of TPNR following EBUS-TBNA using the following search terms - (“ebus” or “ebus tbna” or “tbna” or “endobronchial ultrasound” or “endobronchial ultrasonography” or “endobronchial ultrasound guided” or “endoscopic ultrasound” or

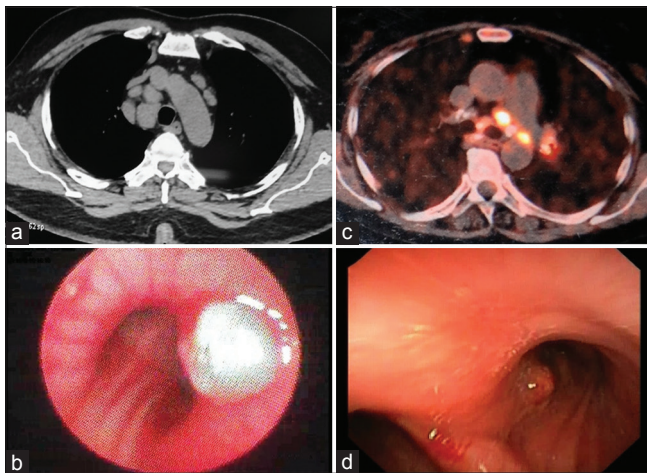


Figure 1: (a) Computed tomography scan of thorax showing enlarged homogenous lower right paratracheal lymphadenopathy. (b) Flexible bronchoscopy showing a broad-based nodular whitish lesion in right lateral tracheal wall at the site of endobronchial ultrasound-guided transbronchial needle aspiration puncture site. (c) Fluorodeoxyglucose-positron emission tomography-computed tomography scan showing fluorodeoxyglucose avid mediastinal lymph nodes at the bilateral lower paratracheal and subcarinal stations. (d) Flexible bronchoscopy showing endobronchial nodule in proximal right main bronchus at subcarinal location, at the site of endobronchial ultrasound-guided transbronchial needle aspiration puncture site

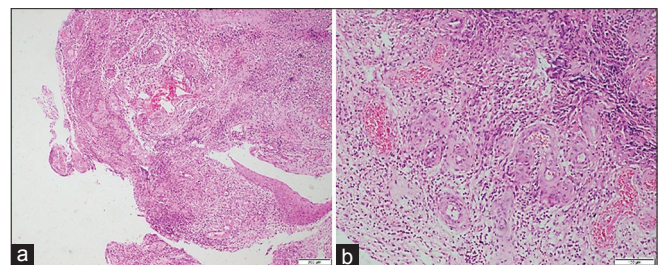


Figure 2: Histopathological examination findings from the biopsied tracheobronchial puncture-site nodular reaction (a) ulceration of the lining epithelium with sprouting of the capillaries and inflammatory cells (H and E, $\times 4$). (b) High power shows proliferating capillaries, edematous stroma, and chronic inflammatory cell infiltrate (H and E, $\times 20$)

“transbronchial needle aspiration”] and [“granulation” or “polyp” or “endobronchial mass” or “endobronchial polyp” or “endobronchial inflammatory polyp” or “endobronchial granuloma” or “granuloma”]. We also reviewed the reference lists of the published studies and also searched through our personal files. We included case reports and original articles describing TPNR as a complication of EBUS-TBNA. Review articles, comments, editorials, abstracts, and articles not related to EBUS were excluded from the study. Any disagreement between authors was resolved by consensus. The database created from the electronic searches was enlisted in reference manager software (endnote), and duplicate citations were removed. Relevant studies were finally shortlisted after screening of the titles and the abstract, and the detailed systematic review methodology is summarized in Figure 3. Full texts of all the qualifying articles were retrieved and studied in detail. The following information was extracted: (a) publication details (authors, year of publication), (b) patient demographics (age, sex), (c) indication of EBUS-TBNA, (d) LN station sampled, needle gauge, and diagnosis on EBUS-TBNA, (e) duration between EBUS-TBNA and identification of reaction, (f) symptoms at presentation and location of nodule, (g) flexible bronchoscopic description, (h) histopathological examination findings from the nodule, (i) treatment offered, and (j) follow-up if available.

The details of the studies finally shortlisted for inclusion are summarized in Table 1.

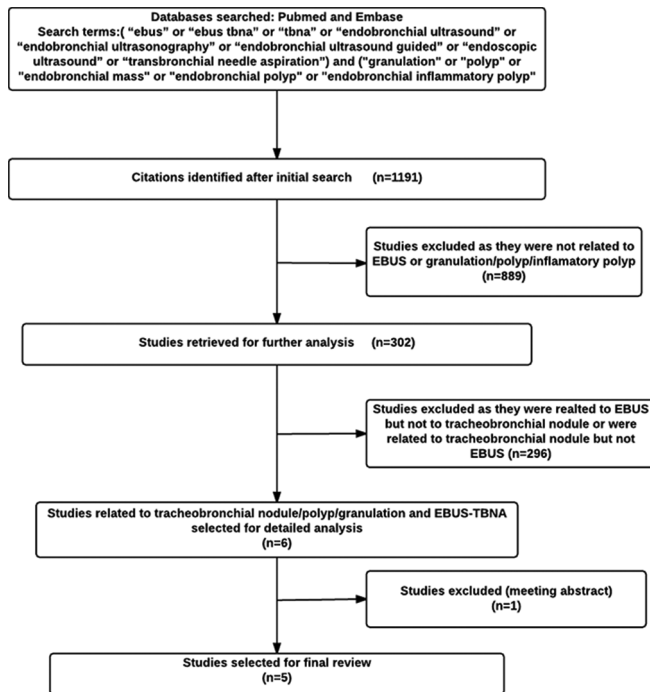


Figure 3: Methodology of the systematic review of studies describing the occurrence of TPNRs following endobronchial ultrasound-guided transbronchial needle aspiration

DISCUSSION

With increasing performance of EBUS-TBNA worldwide, it is likely that the complications related to the procedure shall be increasingly identified and reported. Although EBUS-TBNA has excellent safety profile (rate of complications [0.15%–1.44%] and mortality [0.01%–0.08%]), numerous complications have been described in the literature.^[4,10] One of the rarely described phenomena following EBUS-TBNA is the formation of nodular reactions at the tracheobronchial puncture sites.

Our systematic review of the literature identified five studies (all case reports) describing six patients wherein a TPNR occurred following EBUS-TBNA.^[5-9] The clinical diagnosis was suspected malignancy in four patients and TB in two patients. A 22-gauge EBUS-TBNA needle was used in three patients whereas the needle gauge was not reported in three patients. Diagnosis following EBUS-TBNA was TB in four patients, reactive lymphadenitis in one patient, and malignancy in the remaining one patient. Time to the identification of TPNR was variable and ranged from 2 to 6 months. In three of the six patients (50%), development of TPNR was associated with development of new symptoms related to the same while remaining three patients were asymptomatic. The location of TPNR was right paratracheal in four patients (lower paratracheal in three and upper paratracheal in one) and subcarinal/right main bronchus/right secondary carina in the remaining two patients. Only in one patient, TPNR was large enough to cause significant central airway luminal obstruction. Histopathological examination of the TPNR demonstrated granulomatous inflammation in all the four patients with a diagnosis of TB. Only granulation tissue was identified in the remaining two patients with a final diagnosis of reactive nodes or malignancy. Most cases had single lesion, while in two patients, multiple TPNR were present.^[6,9] TPNR resolved spontaneously or with conservative medical management in three of the six patients (50%) that included rigid bronchoscopy with argon plasma coagulation (APC), cryotherapy, and flexible bronchoscopic biopsy-assisted removal. Recurrence following bronchoscopic removal occurred in one patient.^[8] In that patient, initial presentation of the TPNR was with significant airway obstruction wherein rigid bronchoscopy and APC had been utilized for treatment. It is possible that the effect of bronchoscopic interventions may have promoted the granulation response or it was related to the inherent patient characteristics with propensity to develop aggressive reparative granulation akin to the formation of keloids in the skin. Finally, TPNR resolved in all six patients on follow-up with no complications.

On review of the lesion images in the respective publications, most of the lesions were appearing broad based and not lesions with a thin stalk to suggest a classical polypoidal lesion. Histopathological findings

Table 1: Summary of studies describing tracheobronchial puncture site nodular reaction following endobronchial ultrasound-guided transbronchial needle aspiration

Author (year)	Patient details	Indication for EBUS-TBNA	Lymph node station sampled EBUS-TBNA needle gauge	Diagnosis on EBUS-TBNA aspirate	Symptoms at TPNR identification. Duration since EBUS-TBNA	Location of TPNR	Flexible bronchoscopy findings	Lesion terminology given by authors	Histopathological examination findings from TPNR	Management	Follow-up
Gupta et al. (2010)	32/female. Suspected TB	Right paratracheal lymph node on CT	Lower right paratracheal (4R). Needle gauge-22 gauge	TB (necrosis, AFB+, TBPCR positive)	Cough and dyspnea/CT showed intratracheal mass at lower paratracheal region 2 months	Right paratracheal (4R)	Exophytic nodular lesion in right lower trachea overhanging right main bronchus	Endobronchial Inflammatory polyp	Granulomatous inflammation	Flexible bronchoscopic removal using biopsy forceps	Not reported
Lee et al. (2013)	73/female D/D bone tumor versus TB	FDG avid multiple mediastinal lymph nodes and suprapancreatic nodes, RUL lung nodule; multiple areas of bony FDG uptake	Lower right paratracheal (4R). Needle gauge-22 gauge	TB (necrosis, granuloma). BAL - <i>Mycobacterium</i> TB culture positive bone biopsy - chronic osteomyelitis	Cough and dyspnea/CT - reduction in 4R node size with appearance of endotracheal mass 70 days	Right paratracheal (4R)	Large exophytic nodular endotracheal growth with approximately 70%-80% luminal occlusion	Endotracheal tuberculous granuloma	Tuberculous granuloma with granulomatous inflammation	Rigid bronchoscopy and APC-assisted removal	Recurrence after 140 days; removed using APC Complete resolution on follow-up CT after 9 months
Hata et al. (2013)	26/female. Suspected lung cancer with metastases	FDG avid mediastinal lymph nodes, MRI brain - multiple nodular lesions	Subcarinal (7) and hilar. Needle gauge-22 gauge	TB cytology - caseous necrosis. Scalene lymph node biopsy - <i>Mycobacterium</i> TB on culture and HPE s/o TB	Asymptomatic follow-up routine CT - intrabronchial polypoid lesions at puncture sites 2 months	Subcarina (right side) station 7 and secondary carina (right interlobar 11R)	Nodular lesions with irregular surfaces	Bronchial tuberculosis	Granulomas with foreign body macrophages	Initiation of oral corticosteroids with continuation of anti-tuberculous medications	Resolution on follow-up bronchoscopy after 1.5 months
Kim et al. (2015)	54/male. Bladder carcinoma with suspected mediastinal metastases	Bladder carcinoma with FDG avid mediastinal lymph nodes, RUL lung nodule	Right upper and lower paratracheal (2R and 4R) and left interlobar (11L). Needle gauge - not mentioned	Reactive - anthraco - fibrosis	Asymptomatic - follow-up CT showed right upper paratracheal endoluminal nodular projection. Duration not specified	Right upper paratracheal (2R)	Round mass with irregular, friable surface partly obstructing the lumen of the upper trachea	Endobronchial mass/ endobronchial inflammatory polyp	Granulation tissue and squamous dysplasia	Cryotherapy application followed by antibiotics and steroids	Resolution at follow-up scan, 7 months later
	56/male. Suspected lung cancer with mediastinal involvement	RUL lung mass, right paratracheal and hilar lymph nodes	Right upper and lower paratracheal (2R and 4R). Needle gauge - not mentioned	Metastatic squamous carcinoma	Developed radiation esophagitis, follow-up CT - reduced size of primary mass and nodes; new nodular projection in lower trachea. Duration not specified	Right lower paratracheal (4R)	Round mass with smooth surface in right lower tracheal wall	Endobronchial mass/ endobronchial inflammatory polyp	Granulation tissue	Oral antibiotics	Resolution on follow-up chest CT at 4 months

Contd...

Table 1: Contd...

Author (year)	Patient details	Indication for EBUS-TBNA	Lymph node station sampled EBUS-TBNA needle gauge	Diagnosis on EBUS-TBNA aspirate	Symptoms at TPNR identification. Duration since EBUS-TBNA	Location of TPNR	Flexible bronchoscopy findings	Lesion terminology given by authors	Histopathological examination findings from TPNR	Management	Follow-up
Lee et al. (2015)	29/male. Suspected TB	CT - conglomerated mediastinal lymph nodes - right upper paratracheal, bilateral lower paratracheal, subcarinal and right hilar	Right lower paratracheal (4R) and hilar (10R). Needle gauge - not mentioned	TB AFB+; granulomatous inflammation with necrosis, postbronchoscopy sputum c/s - <i>Mycobacterium</i> TB	Asymptomatic - CT on follow-up showed reduction in node size along with right main bronchus nodule 6 months	Distal right main bronchus and secondary carina (likely 10R and 11R)	Lobulated endobronchial lesions in distal right main bronchus and right secondary carina	Endobronchial inflammatory polyp	Granulomatous inflammation; AFB negative TBPCR negative <i>Mycobacterium</i> TB culture negative	Observation	Complete resolution on bronchoscopic examination after 7 months

AFB: Acid fast bacilli, FDG: Fluorodeoxyglucose; CT: Computerized tomography, HPE: Histopathological examination, TB: Tuberculosis, TB PCR: Polymerase chain reaction test for tuberculosis, BAL: Bronchoalveolar lavage, APC: Argon plasma coagulation, TPNR: Tracheobronchial puncture site nodular reaction, EBUS-TBNA: Endobronchial ultrasound-guided transbronchial needle aspiration, RUL: Right upper lobe, MRI: Magnetic resonance imaging, R: Right, L: Left, FB: Flexible bronchoscopy, c/s - Culture and sensitivity

were not consistent with a classical endobronchial inflammatory polyp as has been previously reported in the literature.^[11] The first report describing a TPNR was by Gupta *et al.*, wherein the authors described the lesion as an endobronchial inflammatory polyp although the histopathological findings demonstrated granulomatous inflammation which is not the histopathological finding in an endobronchial inflammatory polyp as has been highlighted multiple times in the literature previously.^[11-13] Owing to lack of an initial standardized definition, TPNR has been defined by described by various terms in the literature previously including endobronchial inflammatory polyp, granulation or granuloma formation, based on either morphologic or histologic characteristics. TPNR appears to be a valid definition as this takes into consideration the fact that first, the antecedent stimulus is EBUS needle puncture and these lesions develop at the same site. Second, the morphologic appearance resembles a nodule and does not conform to the classical description of polyp. Third, histology may differ from inflammatory granulation tissue (due to puncture trauma and ensuing inflammatory reaction) to spread of nodal disease through puncture tract (e.g., granulomatous inflammation). Thus, a classification into granulomatous and nongranulomatous varieties should be adopted for future description of such reactions. In our patient one, the histopathological examination demonstrated granulation tissue alone when the final diagnosis was TB. This is the first report of the development of nongranulomatous TPNR in a patient with tuberculous lymphadenitis. TPNRs may represent an abnormal airway reparative response in reaction to the tracheobronchial mucosal break in the nongranulomatous variety or the extension of underlying tuberculous lymphadenitis akin to epituberculosis in granulomatous variety.

As it is not a routine to perform a follow-up bronchoscopy evaluation in patients following EBUS-TBNA, it is possible that this entity may be significantly underrecognized. In both our patients, a conservative approach led to the resolution of the TPNR and that has been the case with most of the previously reported cases. Therefore, from a therapeutic perspective, a very aggressive interventional bronchoscopic approach to hasten TPNR resolution may not be warranted. Bronchoscopic removal of TPNR should only be considered in patients wherein the TPNR is causing or is likely to cause symptomatic central airway obstruction. Symptomatic patients may require removal under flexible or rigid bronchoscopy using electrocautery, APC, or cryotherapy. For asymptomatic cases, observation along with treatment of the primary disease (e.g., antitubercular therapy, antibiotics) may result in complete resolution.

Another important consideration is the fact that in patients wherein EBUS-TBNA is performed for diagnosis or staging of malignancy, TPNR can be confused with tumor metastasis at the puncture site.^[7] In one of our patients, (Case 2) TPNR was initially considered as

a metastatic nodule. However, biopsy demonstrated granulation tissue, without any atypical cells or granuloma.

CONCLUSION

TPNRs are a rarely reported complication of EBUS-TBNA which can be of granulomatous and nongranulomatous varieties. Most of these have a benign course and may improve with conservative medical management alone. These nodular reactions should be considered as one of the differential diagnosis of an endobronchial nodular lesion during evaluation of patients who have previously undergone EBUS-TBNA.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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