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Original contribution

Pulmonary pathologic alterations associated with biopsy inserted hydrogel plugs☆

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Summary The prevention of pneumothorax after percutaneous lung biopsy is a major patient safety concern. The insertion of hydrogel plugs into biopsy sites to mitigate this complication is a new intervention. The histology of the plug has not been previously reported, and in this study the histologic reaction is reported in 13 cases. The hydrogel plug forms a spherical basophilic matrix pool with an adjacent foreign body giant cell reaction and patchy eosinophilia. No extension to the pleural surface is present. The potential diagnostic errors related to the presence of the plug are discussed.

1. Introduction

Computed tomographic guided percutaneous biopsies of lung nodules are a routine diagnostic procedure in the evaluation of solitary pulmonary masses. Over time, complications of this procedure have been minimized but still include a real risk of pneumothorax with secondary life complicating and expensive interventions including chest tube placement, repeat radiographic examinations, thoracentesis, and hospitalization. In order to reduce complications, efforts have been made to reduce postbiopsy pneumothoraces and have included the insertion of autologous fibrin plugs, Gelfoam slurries, fibrin glue, and most recently polyethylene glycol hydrogel plugs [1-7]. All options reduce the pneumothorax risk although experimental studies suggest that hydrogels provide the greatest tethering effect at the edges of the biopsy tract. The histomorphologic findings of hydrogels have not been reported and this precipitated diagnostic confusion in a sentinel case at our institution that led to this study of 12 other cases in which a hydrogel plug was inserted and a post biopsy resection of the lung occurred.

2. Materials and methods

Thirteen patients underwent sequential computerized tomographic biopsy of the lung with the insertion of a hydrogel plug (Biosentry Tract Sealant System; Surgical Specialties Corporation; Wyomissing, PA) and based on biopsy results and clinical evaluation underwent a subsequent surgical

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resection. The surgical resections form the basis of this short report.

All biopsies were performed by a single interventional radiologist, within department criteria for coagulation studies and platelet counts, as well as withholding of blood thinners. The biopsies were all performed using CT-fluoroscopy with coaxial needle technique with a 19G/20G core needle set (Bard). A 19G guide cannula was inserted to the periphery of the target lesion, and upon removal of the stylet, a 20G core needle was used to obtain tissue. The coaxial technique has the theoretic benefit of making multiple needle passes with a single pleural puncture. Usually two specimens were prepared and assessed for adequacy by a member of the pathology department during the procedure, followed by additional specimens as needed based on the pathologist's recommendation. The total number of samples ranged from 2 to 5. Prior to placing the hydrogel plug, a measurement was obtained from the working images of the distance from the skin to the pleural surface to adjust the depth of the plug pusher, and a minimum distance of 1 cm from pleura to the lesion was also confirmed. The absence of pneumothorax was confirmed based on CT fluoroscopic images limited to the area being biopsied. The plug kit was then opened, consisting of a preloaded cartridge with the plug and the adjustable deployment pusher. The stylet was removed from the 19G guide cannula and saline dripped into the hub to both provide hydration and prevent inadvertent introduction of air into the system. The cartridge was attached to the hub of the cannula with a Luer lock connection and the pusher placed through the cartridge-cannula assembly, resulting in the plug being pushed through the cannula to the desired depth. The cannula was then withdrawn while the pusher remained stationary, resulting in the plug being unsheathed and exposed in the biopsy tract at the desired depth with the majority of the plug within the tract, and a small tail outside the pleural surface.

Routine histologic examination of the resection specimen was performed and included multiple sections of the lung mass (5–7 sections) studied with hematoxylin and eosin stains.

This study was approved by the University of Pittsburgh institutional Review Board (PRO 12070229). See Table.

3. Results

Thirteen patients comprised the study group. Uncomplicated core biopsies were performed with a subsequent insertion of a hydrogel plug from 21–87 days prior to complete surgical resection for five primary lung adenocarcinomas, four primary lung squamous cell carcinomas, and one primary lung small cell carcinoma, one typical carcinoid tumor, and one metastatic renal cell carcinoma, clear cell variant, and one infarct. Average time between biopsy and surgical resection was 45.6 days.

Table Pulmonary pathologic alterations associated with biopsy inserted hydrogel plugs

Case	Age/sex	Diagnosis	Days between biopsy and resection	Site	Procedure
1	69/M	SQ CA	25	RUL	L
2	69/F	SCCa	45	RLL	L
3	59/F	AD CA	87	RML	L
4	74/M	AD CA	51	RUL	S
5	56/M	AD CA	55	RUL	L
6	53/M	Metastatic renal CA	21	RUL	S
7	55/F	Carcinoid	47	LUL	S
8	64/F	AD CA	44	RUL	S
9	82/F	SQ CA	33	LLL	L
10	74/M	SQ CA	56	LUL	S
11	79/M	SQ CA	27	LLL	S
12	66/F	AD CA	66	RUL	L
13	68/F	Infarct	35	LUL	S

Abbreviations: M, male; F, female; SQ CA, squamous carcinoma; AD CA, adenocarcinoma; SCCa, small cell carcinoma; RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LLL, left lower lobe; LUL, left upper lobe; L, lobectomy; S, segmental resection.

In all 13 cases a large pool of well demarcated basophilic material was enveloped by a fibrogranulomatous reaction (Fig. 1). At the junction with the basophilic hydrogel plug was a non-necrotizing granulomatous reaction with giant cells and histiocytes that appeared compressed or flattened and surrounded a large basophilic pool of hydrogel. In the majority of the cases the histiocytes had finely vacuolated cytoplasm. In six cases (46%) eosinophils percolated between the macrophages (Figs. 2 and 3). Beyond the thin layer of

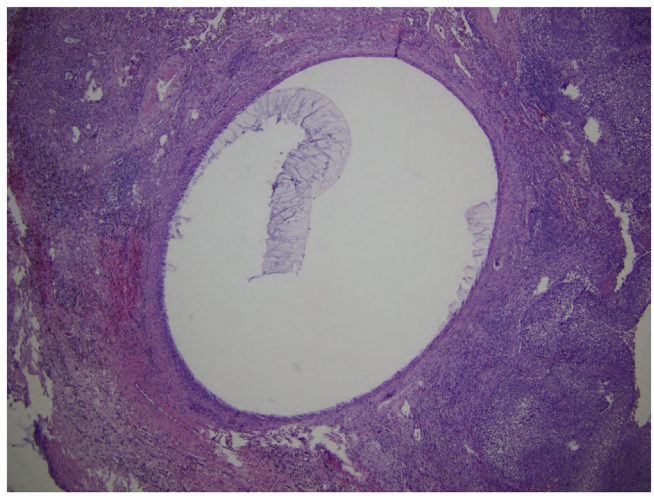

Fig. 1 The hydrogel plug formed a circular cyst filled partially with a basophilic matrix (H&E, ×40).

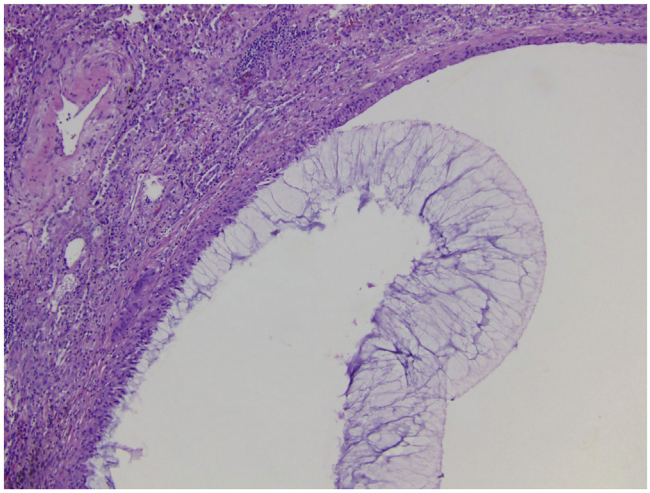

Fig. 2 The hydrogel plug formed a wispy latticework of stringy basophilic webs with an adjacent foreign body granulomatous reaction (H&E ×200).

phagocytic cells was a layer of concentric paucicellular collagen deposits that confined the hydrogel material within a circumferential confined area. No significant granulation tissue reaction was noted although in two cases fibrin exudation around the plug was seen. No evidence of eosinophilic pleuritis or chronic pleural fibrosis was noted in 12 of 13 cases and in no instance was the hydrogel material in continuity with the pleural surface. In only one case was there an eosinophilic pleuritis with subpleural transvascular eosinophilic infiltrates similar to what has been described by Luna, et al [8] in pneumothorax associated vascular inflammation. The presence of eosinophils was not correlated with me after biopsy.

Hydrogel plugs inserted into aggregates of carcinoma cells did not elicit a foreign body granulomatous reaction which was seen only where abundant stromal cells were present.

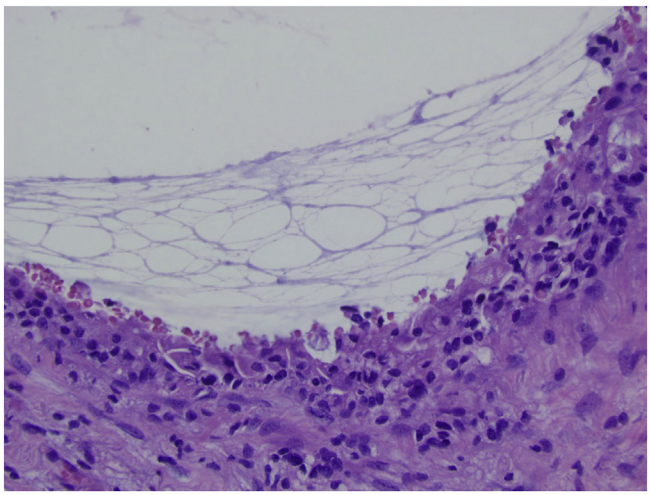

Fig. 3 Hydrogel plug with granulomatous reaction (H&E, ×400).

Histochemical staining of the hydrogel plus was not helpful. The hydrogel plug had a basophilic appearance with hematoxylin and eosin stains and a vague hexagonal matrix like configuration. Periodic acid Schiff staining displayed weak positivity without the tinctorial properties of mucin or glycogen. Mucicarmine stains uniformly showed flocculent mucicarminophilic granular debris lacking the wispy quality of biologic mucin. Trichrome stains demonstrated a brownish discoloration to the material while Congo red, Iron, and elastic tissue stains were negative.

4. Discussion

With patient safety and reduced hospital stay representing two major driving forces in health care, new opportunities to diminish costs have been explored. In an attempt to reduce pneumothorax and its attendant complications after percutaneous biopsy of lung nodules, polyethylene glycol hydrogel plugs have been introduced into the biopsy tract due to their experimental capacity to bind together the margins of the lung after extraction of a core of diagnostic material. In some studies such hydrogel plugs proved superior to other options including autologous fibrin clots, Gelfoam slurries, and fibrin glue [1,2]. The hydrogel plug presents a distinct morphology to the histopathologist and this survey study was intended to make thoracic pathologists aware of this new pathologic "entity" and to help avoid diagnostic pitfalls.

While superficially the hydrogel plug resembled a pool of basophilic mucin as one might see with mucinous adenocarcinoma of the lung or pseudomyxoma peritonei due to abdominal carcinomatosis or mesothelioma, the polyethylene glycol plug has a distinct latticework configuration at higher magnification and in some instances appears as a repetitive hexagonal matrix. While erythrocytes are admixed, the matrix is largely cell free and does not induce a fibrovascular or histiocytic ingrowth into the plug with only a minimal histiocytic foreign body giant cell reaction occurring at the edge of the plug. The histopathologic description of hydrogel plugs inserted into mammals is very limited and in fact we could not find any descriptions beyond nonspecific remarks that there was no morphologic reaction to the exogenous material at 6 months examination in swine [1,2]. Our cases were examined no earlier than 21 days so the acute reaction to the plug insertion is unclear. Certainly though after a couple weeks the plug induces only a foreign body giant cell reaction with some tissue eosinophilia and minimal fibrosis.

Failure to recognize such a plug can precipitate several differential diagnostic concerns for the pathologist, predicated on the observation of pools of extracellular "mucin". This has been well reported in the cytology literature where mucinous material derived from specimen containers, intravascular catheters, or additives to biologic fluids can mimic the histology of a paucicellular mucinous adenocarcinoma, eg, pseudomyxoma peritonei [9-11]. In the lung this may

lead to misclassification of conventional adenocarcinoma as mucinous adenocarcinomas or concerns for infectious complications as described with capsule rich fungal infections such as cryptococcus or in some chronic mycobacterial pseudotumors. With the current focus on immunotherapy, the presence of a granulomatous reaction could conceivably interfere with quantitative assessment of the inflammatory infiltrates focused on infiltrating carcinoma, eg, PD-L1 scores. It is also of some interest that the hydrogel plug does not remain in continuity with pleural space but is incorporated into the lung parenchyma without a pleural reaction.

In summary, this brief report informs surgical pathologists of a relatively new phenomenon in lung resections related to the use of hydrogel plugs into the space vacated by a core biopsy, intended to reduce pneumothorax, which in and of itself induces a granulomatous reaction to pools of basophilic exogenous matrix.

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