

A rare case of Calcified Mediastinal Lymphadenopathy Due to anal Adenocarcinoma Metastasis.

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Abstract: Introduction: Anal cancers constitute 1.5% of all gastrointestinal malignancies. Intrathoracic lymph nodal calcification is thought to be sequelae of prior granulomatous diseases, however, it is a known predictor of metastasis from various primaries. We describe a case of anal adenocarcinoma with multiple calcified metastatic mediastinal lymphadenopathies.

Case Details: A 43-year-old female presented with bleeding per rectum and chest pain for 1 month. Digital per rectal examination revealed thickened anal wall. Contrast-enhanced computed tomography (CECT) of the pelvis showed irregular circumferential wall thickening in the anal canal. CECT of the thorax showed multiple calcified mediastinal lymphadenopathies. Serum calcium level was normal. Proctoscopy-guided biopsy from the anal canal was reported as adenocarcinoma. PET-CT (Positron Emission Tomography-computed tomography) showed uptake in the proximal anal canal and mediastinal lymph nodes. Endobronchial ultrasound-guided fine needle aspiration was reported as metastatic adenocarcinoma. Finally, it was found to be a case of well-differentiated adenocarcinoma of the anal canal with multiple calcified metastatic mediastinal lymphadenopathies.

Discussion: Metastasis in anal carcinoma is seen only in 10% of cases, of which the most common is in the liver and lungs. Calcified mediastinal lymph nodes are manifestations of previous granulomatous infection but are rarely due to metastasis from mucin-producing adenocarcinomas. Interestingly in our case, after the biopsy confirmation of anal adenocarcinoma, PET-CT showed mediastinal nodal uptake rather than other solid organs or pelvic or inguinal lymph nodes. There are very few reports of metastases of anal cancer to mediastinal nodes in the literature. We did a thorough web search and as far as we know, this is the first case report on calcified metastatic mediastinal lymphadenopathies from anal adenocarcinoma. **CONCLUSION:** If calcified mediastinal lymph nodes are found in the CECT thorax, apart from benign conditions, metastasis from the lower gastrointestinal tract malignancies should be in the working differentials and hence pathological examination of calcified nodes becomes mandatory.

Key words: Anal adenocarcinoma, Mediastinal lymphadenopathy, Gastrointestinal Malignancies, EBUS, PET-CT.

INTRODUCTION

Anal cancers constitute <5% of all gastrointestinal malignancies [1]. Most of them are squamous cell carcinomas arising from the non-keratinized squamous epithelium below the dentate line. While adenocarcinomas (ADCs) are 20%, melanomas, and small cell carcinomas are the least commonly occurring anal carcinomas [2]. Intrathoracic lymph nodal calcification has long been thought to be the sequelae of prior granulomatous diseases and hence as such has been thought to be a sign of benignity. However, lymph node calcification is a known predictor of metastasis from various primaries, such as squamous cell carcinoma of the head or neck, papillary thyroid carcinoma, and adenocarcinoma of the rectum or colon. Hereby we describe a case of anal ADC presented with calcified metastatic mediastinal lymphadenopathies.

CASE DETAILS:

A 43-year-old female, homemaker, never smoker, presented with chest pain for 1 month. Chest pain was dull aching type, central, and non-radiating without palpitations, giddiness, or syncope. The patient neither had a history of exposure to silica dust nor had contact with an active tuberculosis case. She had no prior malignancy. She gave no history of any skin changes or swelling in any part of the body. Electrocardiography and echocardiography were normal. Digital per rectal examination showed thickened anal wall. Chest roentgenography was normal. CECT of the thorax showed multiple mediastinal lymphadenopathies in

bilateral lower paratracheal, subaortic, para-aortic, subcarinal, and bilateral hilar regions (stations 4R and 4L, 5, 6, 7, 10R, and 10L) with dense punctate internal calcific foci (Figure 1a). Serum calcium levels with albumin correction were normal. On further inquiry, she also gave a history of bleeding per rectum, 2 episodes, 2 months back for 2 days.

Figure 1a:

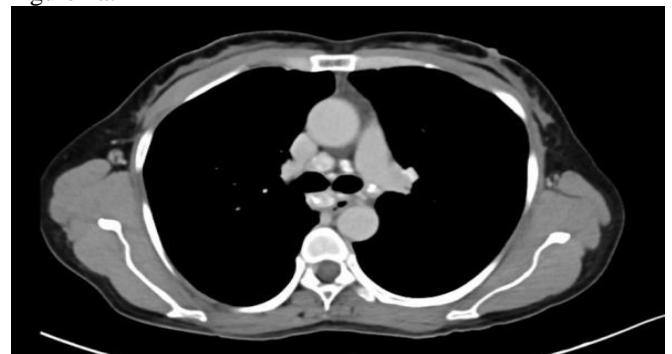


Figure 1a - Enlarged mediastinal nodes (lower paratracheal, sub aortic, para-aortic, subcarinal and hilar nodes) showing dense punctate internal calcific foci.

Digital per rectal examination was done which suggested thickened anal wall. CECT of the pelvis was done which showed irregular heterogeneously enhancing circumferential wall thickening in the distal rectum and anal canal for a length of 4.8 cm with loss of fat planes to the vagina. Positron emission tomography-computed tomography (PET-CT) showed metabolically active disease in the proximal anal canal with few sub centimetric metabolically inactive mesorectal lymph nodes and metabolically active focuses in

the body of L5 vertebra and mediastinal lymph nodes (Figure 1b).

Figure 1b:

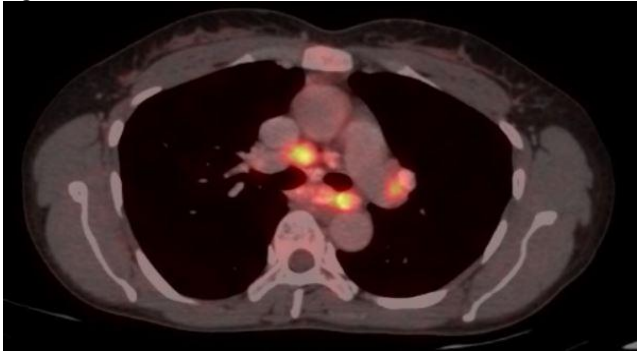


Figure 1b - PET-CT showing metabolically active disease in multiple mediastinal nodes.

Proctoscopy guided biopsy from the anal canal showed a tumor arranged as back-to-back tubular glands which were lined by moderately pleomorphic columnar cells with stratification with evidence of muscularis mucosa invasion, reported as well-differentiated adenocarcinoma (Figure 2a and 2b).

Figure 2a and 2b:

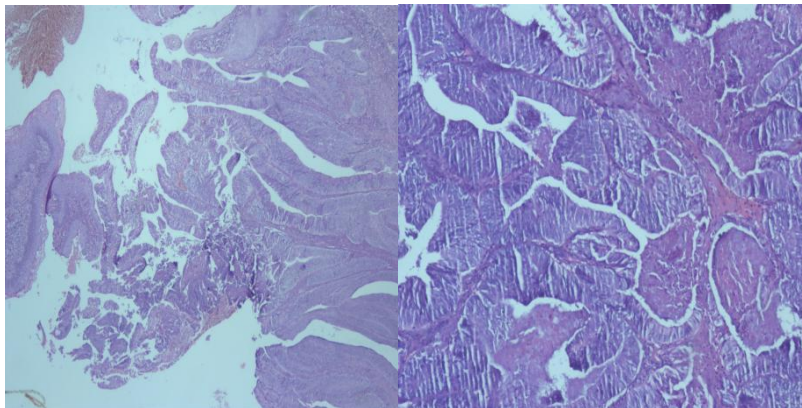


Figure 2a - Sections show anal squamous epithelium with underlying polypoidal lesion lined by dysplastic glands arranged back-back in a tubulo-villous pattern (H&EX40). Figure 2b showing dysplastic glands exhibiting stratification and high-grade dysplastic features and intra luminal necrotic debris (H&EX100).

On immunohistochemistry (IHC), cytokeratin 7 (CK7) was negative, whereas CK20 and CDX2 were positive, confirming the colorectal phenotype. Check flexible bronchoscopy revealed normal trachea-bronchial anatomy. This was followed by endobronchial ultrasound (EBUS) guided fine needle aspiration (FNA) of mediastinal lymph

nodes (station 7 and 4R) which showed tumor cells in clusters and glandular pattern exhibiting moderate nuclear pleomorphism, reported as metastatic adenocarcinoma (Figure 2c, 2d and 2e) which was also positive for CK20 and CDX2.

Figure 2c, 2d and 2e:

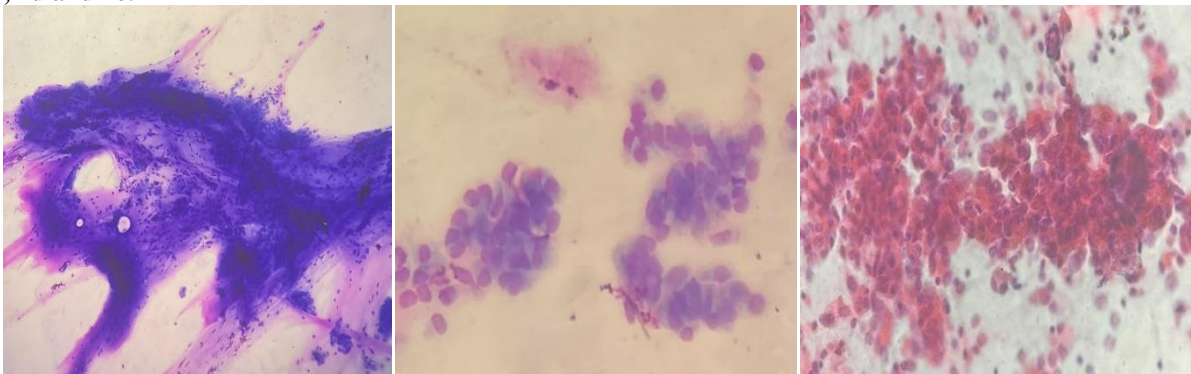


Figure 2c: EBUS guided FNAC from sub-carinal lymph node shows tumor cells in clusters and glandular pattern exhibiting moderate nuclear pleomorphism, admixed with many benign bronchial epithelial cells in the mucoid background (MGG 100X), Figure 2d: shows tumour cell in gland formation (MGG 400X), Figure 2e: PAP 400X (MGG- May Grunwald-Giemsa Stain, PAP- Papanicolaou Stain).

Finally, the patient was diagnosed to have well-differentiated colorectal type of adenocarcinoma of the anal canal with multiple metastatic calcified mediastinal lymphadenopathies. Informed consent was obtained from the patient prior publication.

DISCUSSION

The anal canal has two parts microscopically as well as macroscopically divided by the dentate line above which is

the columnar crypt forming epithelium which drains into mesorectal, presacral, and internal iliac lymph nodes, and below is the anal squamous mucosa which drains into the inguinal and femoral group of lymph nodes. Adenocarcinoma of the anal canal arises from the epithelium of the anal canal including the mucosal surface, anal glands, and lining of fistulous tracts. Among adenocarcinomas, colorectal and extra mucosal are the two types that arise from above the dentate line and from anorectal fistulas respectively [3]. In this case, it was a proximal anal canal malignancy which is of colorectal type. A key risk factor known to predispose to anal cancer is human papillomavirus infection with strains 16 and 18 [4-6]. Others are immunosuppression, receptive anal intercourse, smoking, multiparity, and cervical or vulval cancer. Evaluation in females includes performing a digital rectal examination, anoscopy, inguinal lymph node assessment, gynecological examination, and magnetic resonance imaging [1]. She had posterior vaginal wall infiltrations on examination and mediastinal nodal involvement making the disease locally invasive as well as metastatic. Only 10% of anal cancer patients exhibit metastasis, and the liver and lungs are the most frequently affected organs. [2]. It has a poor prognosis, with a five-year median survival rate of 10% in males and 20 % in females [2]. Nodes considered regional are mesorectal/inferior rectal, internal iliac, and inguinal nodes. Common iliac or retroperitoneal node involvement is considered metastatic [7]. In our case, it is interesting to note that PET did not reveal any regional nodal involvement; instead, it revealed distant mediastinal nodal uptake.

Calcified mediastinal lymph nodes are most often manifestations of previous granulomatous infection and less often due to other diseases like sarcoidosis, silicosis, amyloidosis, neoplasms, metabolic disease, occupational exposures, or previous therapy [8]. Metastatic calcification of lymph nodes from adenocarcinoma is rare as seen in our case. As far as we are aware, calcified metastatic mediastinal lymphadenopathy from anal adenocarcinoma is not yet reported. The tumors that commonly result in calcified metastases are seen in carcinomas (particularly papillary and mucinous adenocarcinomas), sarcomas (chondrosarcoma, osteosarcoma, osteoclastoma, and synovial sarcoma), and treated metastatic choriocarcinoma [9]. Calcification can develop in metastases of several tumors after radiotherapy or chemotherapy, generally secondary to hemorrhage, necrosis, and degeneration (8). They are characteristically multiple, punctate, fine, and localized. A similar pattern of multiple focal calcifications was present in this patient which pointed toward malignancy. Dystrophic calcifications are glomerulated [10]. Complete calcification is seen in tuberculosis (62%) whereas focal eggshell calcification is seen in sarcoidosis (58%) [11,12].

The presence of tumoral calcification is a characteristic finding of mucin-producing adenocarcinomas. There have been cases reported on calcified metastatic mediastinal lymphadenopathy from the primaries of the lung, liver, lymph nodes, spleen, peritoneum, stomach, colon, appendix, ovary, rectum, and biliary tree [10]. This is the first case report of calcified metastatic mediastinal nodes from an anal

cancer that has ever been published. When a patient has a malignancy with calcified nodes, it can be difficult to decide whether to take a sample of those nodes or not because the most prevalent cause of calcified mediastinal nodes is a granulomatous disease's sequelae. This is especially true if the patient has a history of tuberculosis or sarcoidosis. PET-CT can be used to expose the activity of disease within a node but differentiating inflammation and malignancy becomes difficult [13,14]. Therefore, if PET shows nodal activity in a patient with adenocarcinoma who also has a history of granulomatous illnesses, it is crucial to sample the nodes. The patient was initiated on palliative treatment as it was proven to be a metastatic disease.

CONCLUSION

With this, we would like to conclude that calcified mediastinal nodes need not always be of granulomatous or infectious origin. Anal adenocarcinoma metastasis may skip regional nodes and involve mediastinal nodes which may calcify. Hence it is necessary to sample the calcified mediastinal nodes in a patient suspected to have a malignancy of GIT (Gastrointestinal Tract) or diagnosed to have adenocarcinoma of the GIT for histopathological examination to diagnose, stage, and treat the disease appropriately.

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Clinical Practice Points:

- As far as we know, anal adenocarcinoma-related calcified metastatic mediastinal lymphadenopathy has not yet been recorded.
- Anal adenocarcinoma metastasis can skip local nodes and may involve only mediastinal nodes that may calcify.
- Calcified mediastinal nodes are not invariably granulomatous or infectious in origin.
- Therefore, to diagnose, stage, and treat the disease, sampling the calcified mediastinal nodes becomes mandatory in a patient suspected of having a malignancy of the GIT (Gastrointestinal tract) or diagnosed with adenocarcinoma of the GIT.

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Supplement files:

1. Algorithm for various causes and types of calcifications in metastatic mediastinal lymphadenopathy.
2. Table showing differentiating features of various causes of calcified mediastinal lymph node.

Algorithm for various causes and types of calcifications in metastatic mediastinal lymphadenopathy:

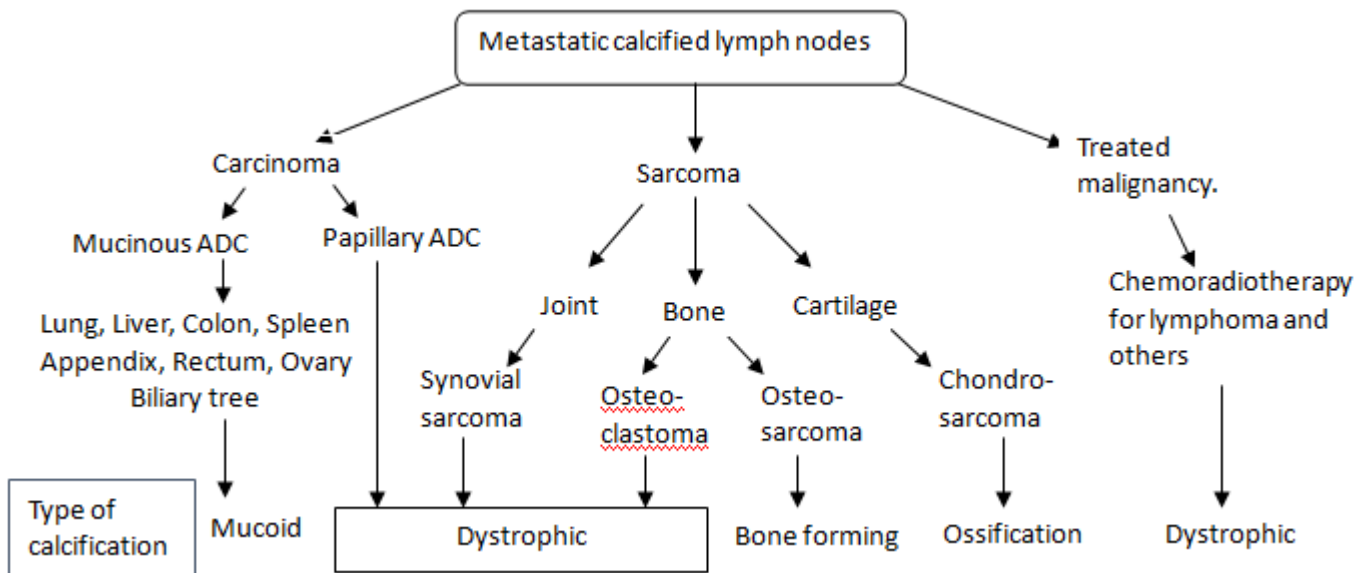


Table showing differentiating features of various causes of calcified mediastinal lymph node.

DISEASE	CLINICAL FEATURES	BRONCHOSCOPIC TECHNIQUE		CYTO/ HISTOPATHOLOGY	TREATMENT	
		MEDIASTI-NUM	LUNG PARENCHYMA		MEDIASTINAL DISEASE	PULMONARY/ SYSTEMIC DISEASE
Tuberculosis	Constitutional symptoms Cough, Chest pain	EBUS-TBNA	BAL ± TBLB	Necrotizing granulomatous inflammation, caseous necrosis, multinucleated giant cells	Tubercular mediastinal lymphadenitis -ATT	ATT / Steroids
Sarcoidosis	Constitutional symptoms Cough, Chest pain, skin and joint lesions	EBUS-TBNA	BAL, EBB, TBLB	Noncaseating epithelioid granulomas, Schaumann bodies, Asteroid bodies	Pulmonary sarcoidosis stage-2 - Steroids	Steroids Lung transplantation
Silicosis	Constitutional symptoms cough, dyspnea	-	-	Fibroblasts and histiocytes with abundant silica, hyalinized and condensed collagen	Mediastinal lymph node silicosis - Avoid exposure	Lung transplantation
Histoplasmosis	Fever, cough, chest pain	EBUS-TBNA	BAL ± TBLB	Small uniform oval, narrow based budding yeasts. Granulomatous immune response	Mediastinal histoplasma granuloma Antifungal: Amphotericin B	Antifungal: Amphotericin B
Metastatic adenocarcinoma	Chest pain, dyspnea, Swelling and symptom due to primary disease	EBUS-TBNA	BAL, EBB, TBLB	Depends on tumor cells of origin	Mediastinal nodal metastasis - Surgery/ Chemotherapy	Surgery/ Chemotherapy
Amyloidosis	Exertional dyspnea, fatigue	EBUS-TBNA	BAL, TBLB	Amorphous eosinophilic deposits that show apple green birefringence under polarized light	Amyloid lymphadenopathy - Observation/ Surgical excision	Stem cell transplant, Immunotherapy
Lymphoma	Constitutional symptoms, SVC syndrome, effusion	EBUS-TBNA / Core biopsy	-	Depends on cell type and subtype	Primary mediastinal lymphoma - Chemotherapy	Chemotherapy
Fibrosing mediastinitis	Dysphagia, dyspnea, SVC syndrome	-	-	Large amounts of concentrically deposited acellular collagen that obliterates adipose tissue.	Fibrosing mediastinitis - Resection of fibrosed or stenosed tissue grafting and stenting.	-
Castleman disease	Constitutional symptoms, Hepatosplenomegaly	EBUS-TBNA	-	Hyaline vascular variant (HVCD) , plasma cell variant (PCCD) and mixed type	Unicentric mediastinal Castleman disease – Surgery	Rituximab Tocilizumab