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Spontaneous infarction of papillary thyroid carcinoma in sickle cell trait patient leading to missed diagnosis on fine-needle aspiration cytology

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ABSTRACT

Papillary thyroid carcinoma (PTC) is a common thyroid malignancy in adults and children. With classical microscopic features seen, fine-needle aspiration cytology (FNAC) is a cost-effective and less invasive procedure to diagnose thyroid lesions. Post-FNAC infarction is common in PTC and other solid benign and malignant lesions. Spontaneous infarctions in various organs are seen in sickle cell disease and trait patients in hypoxic conditions. Aspiration of only necrotic material and no distinct microscopic features cause problems in diagnosis. Infarction should be kept in mind while reporting aspirates from sickle cell patients.

Key words: *Fine-needle aspiration cytology, Infarction, Papillary thyroid carcinoma, Sickle cell trait*

Papillary thyroid carcinoma (PTC) is the most common type of thyroid malignancy, more common in females than the males at the mean age of 40 years. Fine-needle aspiration cytology (FNAC) is cost-effective, less invasive, and widely accepted procedure for diagnosing thyroid lesions. PTC shows cellular smears showing syncytial aggregates and sheets of cells with a distinct anatomical border, focal nuclear crowding and overlapping, and papillary tissue fragments with or without fibrovascular core. Nuclei are ovoid with finely granular powdery chromatin. The typical nuclear features necessary for diagnosis are ground glass (optically clear nuclei) chromatin evident on paraffin-embedded material that may be absent in frozen sections and cytology smears. Nuclear pseudoinclusions, grooves can be seen on cytology [1]. Mitosis is scanty. More than half of the cases show extensive fibrosis in the form of sclerohyaline to highly cellular stroma on histology [2,3]. Background shows scanty, viscous, thick ropy, stringy colloid (chewing gum colloid) in the form of strands, or chunks of dense darkly blue colloid in May-Grünwald–Giemsa stain. Squamoid or histiocytes such as metaplastic cells, psammoma bodies, macrophages, and debris can variably be seen. With these characteristic cytological features, it is easy to diagnose PTC on cytology adequate smears. Post-FNAC partial or complete infarction of thyroid lesions is well known complication, especially in papillary carcinoma [4-6]. We report a case of spontaneous partial infarction in PTC, leading to missed diagnosis on FNAC in a sickle cell trait (SCT) patient.

CASE REPORT

A 65-year–old male patient presented with swelling in thyroid region since 2 years, gradually increasing. The patient had no history of difficulty in swallowing, breathing, change in voice, loss of weight, or appetite. On examination, nodular, firm nontender swelling of 3 cm × 2 cm × 2 cm was seen. Thyroid profile tests were within normal limits. Ultrasonography (USG) showed large well defined multiloculated, heterogeneous mass in posteroinferior portion of the right lobe of thyroid showing coarse calcification. Multiple hypoechoic areas were noted in both lobes. These hypoechoic areas were not taking vascularity, suggestive of colloid cystic degeneration. Pathological correlation was suggested.

USG guided FNAC smears yielded thick hemorrhagic aspirate. Smears showed abundant necrotic material, inspissated ropy, chewing gum colloid, inflammatory cells, cystic macrophages, and plenty of apoptotic follicular cells. FNAC repeated again showed similar morphology (Fig. 1). Considering the necrotic material, prior history of FNAC was asked. The patient had not undergone FNAC previously. Cytological features suggestive of PTC were only these large chunks of colloid. Cytological diagnosis of probable neoplastic origin was given. Considering clinical and radiological suspicion of the neoplastic lesion in elderly male patient, total thyroidectomy was done. SCT status of the patient was not known before surgery. We received a gross specimen of size 5 cm × 4 cm × 3 cm with multinodular external surface. Cut surface showed two nodules with cystic areas. One was partly necrotic pinkish and another yellowish-white with papillary excrescences seen in both nodules. Normal thyroid tissue was identified at the periphery (Fig. 2).

Histopathology showed multinodular goiter in surrounding thyroid tissue. Tumor mass with extensive fibrosis and focal colloid-filled follicles was seen. Tumor showed complex branching papillae with fibrovascular core. Cells are cuboidal

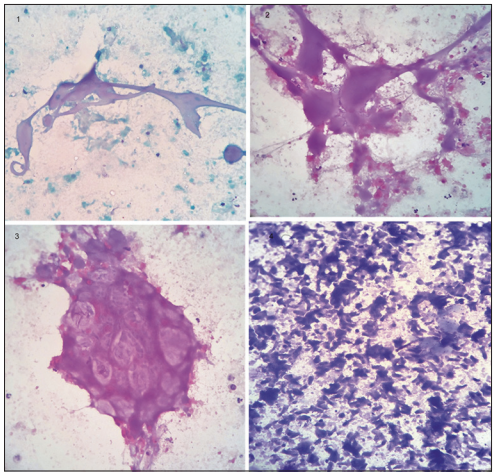

Figure 1: Chewgum colloid and necrosis 1 - pap stain ×40, 2 - H and E ×40, 3 - H and E ×40, 4 - May-Grünwald-Giemsa ×40

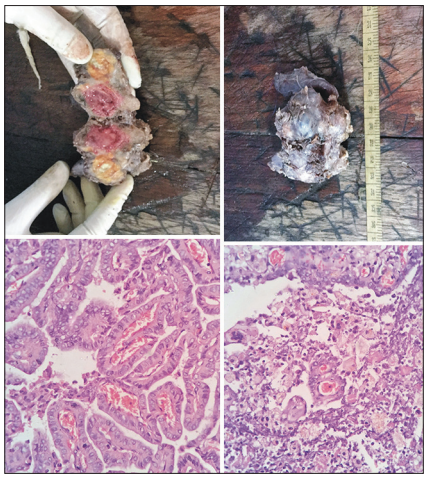

Figure 2: Gross and microscopy, 1 - cut surface large infracted nodule, 2 - external surface nodular, 3 - H and E ×40 papillary architecture, 4 - H and E ×40 histiocytes, giant cell, and papillary core showing sickled red blood cells

with round nuclei showing crowding, overlapping, and ground glass (optically clear) chromatin. Occasional mitosis, psammoma bodies were also seen. There are extensive areas of fibrosis along with chronic inflammatory infiltrate and foreign body giant cells. Large areas of coagulative necrosis with ghost papillae and areas of hemorrhage with sickled red blood cells (RBCs) are seen. Throughout the tumor and normal part of thyroid, the blood vessels are congested and filled with sickled RBC. Diagnosis of well-differentiated PTC with extensive areas of fibrosis and coagulative necrosis was given (Fig. 3).

DISCUSSION

Post-FNAC infarction is well known in some thyroid lesions, especially Hurthle cell neoplasms and PTC. It is also seen in fibroadenoma, phyllodes, pleomorphic adenoma of salivary glands, and other lesions, sometimes causing diagnostic problems in histopathological interpretation [4]. Large area of infarction without prior FNAC is not mentioned in literature. Probable cause of coagulative necrosis in our patient may be the SCT

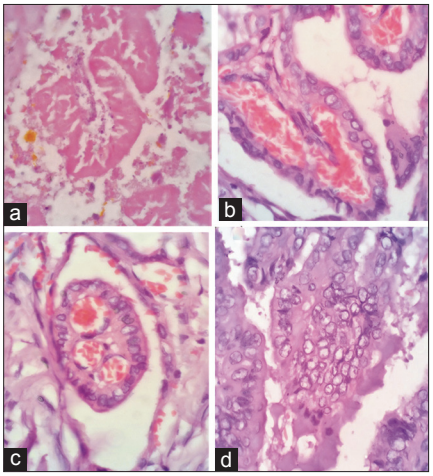

Figure 3: Microscopy a - H and E ×40 infarcted papillae, b - H and E ×100 sickled red blood cells in papillae, c - H and E ×100 vascular emboli, d - H and E ×100 optically clear nuclei and thick colloid

status of patient which was confirmed later on by hemoglobin electrophoresis. Viable tumor cells were not sampled both the times in FNAC.

In hemoglobin S, a point mutation in the gene for the beta-globin chain substitute valine for glutamic acid at the sixth amino acid. This single change generates a structurally abnormal molecule that polymerizes under conditions of deoxygenation. That transforms the cytoplasm into a rigid filamentous gel and leads to the formation of less deformable sickled erythrocytes that result in obstruction of the microcirculation, with subsequent tissue hypoxia and ischemic injury in many organs. The vicious cycle of hypoxia, sickling, thrombosis, ischemia, and infarction resulted in the extensive tumor necrosis.

Many authors put forth hypotheses that intratumoral deformation of erythrocytes was attributed to hypoxic conditions detected in the microvasculature of SCT patients [7,8]. Milosevic et al. hypothesized that focal areas of hypoxia in the tumor coupled with long transit times in the abnormal structures of the microcirculation would be sufficient to trigger sickling of vulnerable erythrocytes in SCT carriers; although it is possible that sickling in tumors might have been attributable to *ex vivo* conditions. High or low temperatures and prolonged drying time of tissue are two such factors that might produce false-positive changes in RBC morphology [8]. Brown et al., however, reported *in vivo* evidence that sickled RBCs preferentially aggregated in the vasculature of tumor relative to normal tissue based on magnetic resonance imaging scans of radiation-labeled RBCs [9].

Obliteration of microvasculature with irreversibly sickled RBCs is seen in vaso-occlusive crisis in both diseased and trait patients in hypoxic states. Patchy renal papillary necrosis is common complication due to hypoxic hyperosmolar milieu in renal medulla. Infarction can be seen in lungs, brain, spleen, liver, and penis in diseased patient. Infection, dehydration, and acidosis can act as triggers, but in most instances, no predisposing cause is identified. Compared to all the benign manifestations of sickle cell, renal medullary carcinoma is a rare and aggressive tumor that is seen almost exclusively in

young patients with SCT. The tumor arises from the epithelium of the distal collecting ducts and grows in an infiltrative pattern, invading the renal sinuses. PTC is not frequently associated with sickle cell status. However, extensive tumor necrosis due to intratumoral sickling may lead to a diagnosis of high-grade tumor in a low-grade malignancy and rapid deterioration of the patient as noted by Agrawal et al. [10].

CONCLUSION

Infarction in FNAC material should be kept in mind while reporting in sickle cell patient whether diseased or trait. Many heterozygous individuals are asymptomatic and prior sickle cell status may not be known. In case of tumor infarcts, search should be made for sickled RBCs and a beforehand investigation by hemoglobin electrophoresis in the region where the prevalence of sickle cell gene is very high. Tumor infarcts may lead to repeated aspiration of only necrotic material, leading to a missed diagnosis of tumor on FNAC.

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