

Incidental thyroid uptake during ^{99m}Tc -methylene diphosphonate bone scintigraphy in oncologic patients

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ABSTRACT

Introduction: Extraosseous accumulation of ^{99m}Tc – methylene diphosphonate (MDP) may be due to neoplastic, dystrophic, hormonal, inflammatory, ischemic, traumatic or excretory disorders. ^{99m}Tc -MDP incidental thyroid uptake is not frequent and is possibly caused by the presence of dystrophic or metastatic calcification, biopsy procedure and presence of benign or malignant thyroid nodules. To analyze the etiological factors leading to ^{99m}Tc -MDP uptake in the thyroid gland.

Methods: Fifty patients (pts), 19 females (38%) and 31 males (62%), 62 ± 12 years, with no previous history of thyroid disease, were included in the study. In the period January 2016 – January 2018, all pts underwent MDP bone scintigraphy due to oncologic indication and incidental tracer uptake was noted in the region of the thyroid gland. Ultrasonography (US) was performed in all pts. Patients with detected nodules underwent ^{99m}Tc -pertechnetate scintigraphy and fine needle aspiration cytology (FNAC). Thyroid hormone and autoantibodies levels were also analyzed. SPECT/CT procedure was performed in all patients to precisely localize the MDP uptake.

Results: Thirty-nine patients had calcifications in the thyroid gland (29 with microcalcifications and 10 with macrocalcifications). In 23 patients, thyroid nodules were detected. ^{99m}Tc -pertechnetate scintigraphy presented 15 cold nodules and 8 nodules with increased tracer uptake. FNAC in 3 patients presented nuclear anisocariosis, with Hurthle cell metaplasia, and surgery was advised. In 11 patients, thyroid cartilage calcifications were detected.

Conclusion: Incidental findings of thyroid ^{99m}Tc -MDP accumulation during bone scintigraphy indicate presence of additional, previously unexpected, active disease processes.

Key words: Bone scintigraphy; Thyroid gland; Incidental ^{99m}Tc -MDP uptake

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INTRODUCTION

Imaging with bone specific radiolabeled tracers can often lead to discovery of incidental unexpected soft tissue uptake. Findings like this indicate presence of calcium deposition outside the skeletal system – process known as soft tissue calcification [1]. Incidental extraosseous uptake seen on ^{99m}Tc – MDP bone scan is not unusual and contributes in proper patient management by revealing previously unexpected diseases, thus improving the adequate therapeutic approach [2].

^{99m}Tc-MDP bone scintigraphy is performed in a number of conditions including primary bone malignancies, metastatic diseases that have spread to the bone, metabolic and/or hormonal alterations, occult fractures as well as in follow up or response to treatment in some solid tumors like prostate and breast cancers [3]. ^{99m}Tc diphosphonate complex adsorbs at the surface of hydroxyapatite crystals, predominantly in the skeletal system, but in certain non-osseous conditions - neoplastic, hormonal, inflammatory, ischemic, traumatic, excretory and artefactual entities, may demonstrate abnormal soft tissue uptake, thus indicating the presence of unsuspected calcium deposition [4].

^{99m}Tc-MDP thyroid incidental uptake is not very frequent and it is possibly caused by the presence of calcification [5, 6], biopsy procedure [7], anaplastic carcinoma [8] or metastatic soft tissue calcifications in patients affected by primary or secondary hyperparathyroidism [9]. It can also happen to have focal tracer uptake in the thyroid autonomous nodules that is probably caused by nodal calcification. Calcified nodules may show high uptake of this radiopharmaceutical. Calcification within the thyroid may happen in both benign and malignant diseases [10]. It is well known that microcalcifications are associated with thyroid malignancy [11]. Instead, the association between macrocalcifications and thyroid cancer remains still under discussion but it is mainly related to benign disease [12, 13].

The aim of this study was to analyze the etiological factors leading to incidental ^{99m}Tc-MDP uptake in the thyroid gland during bone scintigraphy in oncologic patients.

METHODS

The study was monocentric (single institute), observational, prospective, with predefined inclusion criteria - incidental bone tracer uptake into the thyroid gland during MDP bone scintigraphy due to oncologic indication and no previous known history of thyroid disease and exclusion criteria - previously known history of thyroid disease.

Fifty patients, 19 females (38%) and 31 males (62%), 62±12 years, from the period January 2016 – January

2018 were included in the study. All pts underwent ^{99m}Tc-MDP bone scintigraphy due to oncologic indication and incidental tracer uptake was noted in the region of the thyroid gland (21 patients had prostate cancer, 12 pts- breast carcinoma, 7 pts - lung carcinoma, 3 pts - lymphoma, 3 pts - colorectal carcinoma, 2 pts- endometrial carcinoma and 2 pts had multiple myeloma). All subjects gave a written consent for entering the study.

Planar scintigraphy procedure was performed with 740MBq / 20 mCi tracer activity, injected i.v. into the cubital venous system, and the bone scintigrams were obtained 3 hours post injection, using standard positions (antero-posterior / postero-anterior / lateral). We used dual-headed gamma camera MEDISO DHV Nucline Spirit, with 140 keV photo-peak and low-energy, high resolution (LEHR) parallel collimator. Quality control of the radiopharmaceutical was performed prior injection to avoid presence of free ^{99m}Tc-pertechnetate. The results were analysed by two nuclear medicine specialists, separately, as a blinded method of analysis. Afterwards, the interpretations were compared, and a match in the interpretations was considered as a positive scintigraphy finding for incidental tracer uptake in the thyroid gland.

Ultrasonography (US) with Doppler blood flow perfusion estimation of the thyroid gland was performed in all subjects separately, by two nuclear medicine specialists, both with over 10 years of experience in the field of expertise. For the US we used Phillips H.D. 6, Version 1.1, probe 7,5 Hz.

Patients with detected nodules underwent ^{99m}Tc-pertechnetate scintigraphy (185 MBq/5 mCi tracer activity, images obtained 30 min post injection) and US guided fine needle aspiration cytology (FNAC). Thyroid hormone (FT4, FT3), TSH and autoantibodies levels were also analysed in all pts.

SPECT/CT procedure, using Optima NM/CT 640 GE Health care dual detector/4-slice CT gamma camera, LEHR collimator, 120 views, matrix size 128x128, was performed in all pts, to precisely localise the MDP uptake. Images were reconstructed with slice thickness 2 mm, slice spacing 2 mm and matrix size 512x512.

Regions of interest (ROIs) were selected over the thyroid (accumulated impulses-counts value) and over the sternum (control counts value) in order to determine the intensity of tracer uptake into soft thyroid tissue compared to bone. The ROIs were equal sized. The following scale was used: grade 1 – uptake lower than bone, grade 2 – uptake same as bone, grade 3 – uptake higher than bone [14].

RESULTS

SPECT/CT and US revealed 39/50 patients (78%) with calcifications in one or both of the thyroid lobes (Figure 1 and 2), 29 of which (74%) were

microcalcifications < 2 mm and 10 (26%) were macrocalcifications > 2 mm (Figure 3).

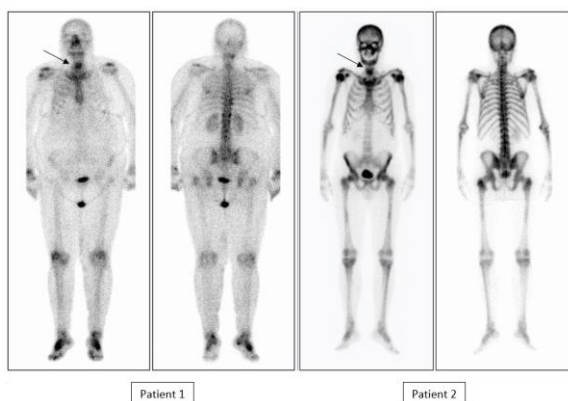


Fig 1. ^{99m}Tc-MDP whole body bone scintigraphy in two patients with incidental uptake in the thyroid gland.

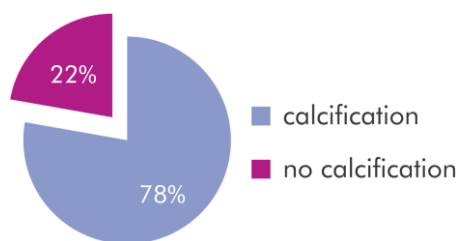


Fig 2. Detected calcifications in one or both of the thyroid lobes.

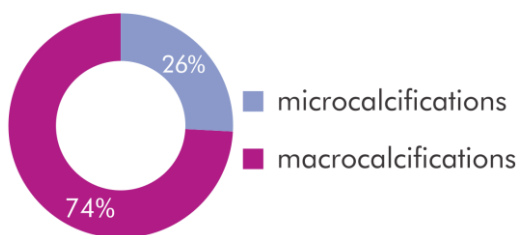


Fig 3. Type of detected calcification.

In 23/50 patients (46%), thyroid nodules were detected, 11 (48%) of which had capsular calcifications (some were with "egg shell" calcifications), and 12 (52%) had intranodal calcifications (Figure 4).

Thyroid scintigraphy with ^{99m}Tc-pertechnetate was performed in all pts where nodules were detected on US and SPECT/CT (Figure 5a), and 15 (62%) nodules were found to be "cold" (without tracer uptake), and 8 (35%) nodules had increased ^{99m}Tc-pertechnetate uptake.

US guided FNAC was performed to all detected nodules, 20 (87%) of which were benign (old classification - group I / Bethesda score - group II) while 3 presented nuclear anisocariosis, with Hurthle cell metaplasia, and surgery was advised (classification group III, IV and V). Postoperative histopathology revealed follicular adenoma in the patient with FNAC classification group III, Hurthle cell thyroid carcinoma in the patient with FNAC classification group IV, and papillary thyroid carcinoma in the patient with FNAC classification group V.

In 11/50 patients (22%), additional thyroid cartilage calcifications were detected on SPECT/CT (Figure 5b).

In 19/50 patients (38%), US detected hypoechoic structure of the thyroid gland with areas of fibrosis, which suggested possible chronic Hashimoto thyroiditis. TSH was elevated and thyroid autoantibodies aTPO and aTg were positive in 14/19 patients (74%), and Levothyroxine substitution was administered. In 13/19 patients (68%), increased blood flow (perfusion and vascularity) of the thyroid gland was noted.

SPECT/CT study in 5/50 cases (10%) detected additional MDP uptake into cervical vertebrae, due to osteophytes and degenerative etiology.

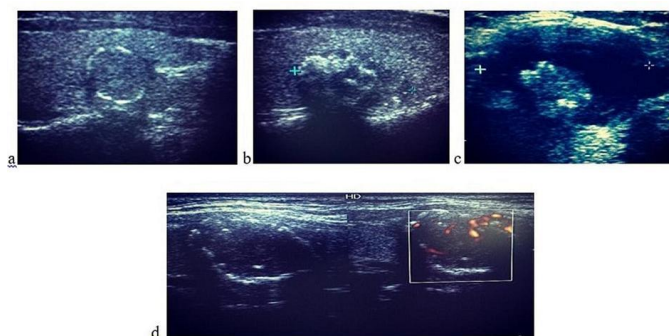


Fig 4. US features of detected nodules with capsular and intranodal calcifications: "egg shell" calcification (a); intranodal macrocalcification (b); intranodal microcalcification (c); and mixed capsular and intranodal calcification (d).



Fig. 5. (a) Planar whole body ^{99m}Tc-MDP bone scintigraphy with incidental uptake into the thyroid gland and metastatic lesion in the left humerus (above) and (b) SPECT/CT detection of ossification of the thyroid cartilage, as well as, MDP accumulation in the right thyroid lobe due to calcified capsule of a thyroid nodule in the same patient (below).

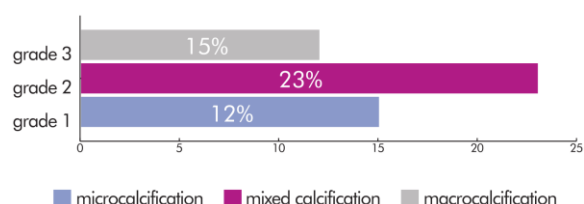


Fig 6. Correlation between the uptake grade and type of calcification.

ROIs comparison presented 12/50 patients (24%) with grade 1 uptake (9 of which had microcalcifications and 3 had Hashimoto thyroiditis), 23/50 patients (46%) with grade 2 uptake (21 of which had benign nodules with mixed micro- and macro calcifications, but predominantly with microcalcifications and 2 had increased vascularity) and 15/50 patients (30%) with grade 3 tracer uptake (9 of which had macrocalcifications, 2 had nodules with calcified capsule and 4 had Hashimoto thyroiditis and additional thyroid cartilage calcifications). Both patients with malignant postoperative findings on histopathology, had grade 3 uptake, which indicates significant positive correlation between the type (grade) of calcification and the diagnostic outcome. The uptake grade presented statistically significant

positive correlation with the type of calcification (micro- or macrocalcification) $p < 0.02$. The higher the uptake grade, the type of calcification changed from micro- into mixed type and macrocalcification (Figure 6).

DISCUSSION

Bone scintigraphy is usually performed to evaluate a wide variety of skeletal abnormalities [15]. ^{99m}Tc-MDP has rapid blood clearance, excellent in vivo chemical stability, and high bone-to-soft tissue ratio, thus, it is ideal for bone imaging [16]. Post i.v. injection, 78% of the tracer dose diffuses from the vascular compartment into the interstitium, with biologic half-life of 2.4 minutes. Any disease process, which is represented with extracellular fluid expansion, may result in increased interstitial bone tracer uptake.

The initial phase of ^{99m}Tc-MDP concentration in soft tissues is directly related to the blood flow intensity and vascularity indicating that processes with increased perfusion (like inflammation) may result in increased tracer concentration. In our study, 19 patients had impaired structure of the thyroid gland on US, indicating possible chronic inflammation – Hashimoto thyroiditis, 14 of which had laboratory

confirmation and 13 of which had increased vascularity and blood flow on Doppler ultrasonography, which according to the above mentioned, could have been the possible mechanism underlying the increased bone tracer uptake into the thyroid gland.

The uptake of the ^{99m}Tc – diphosphonate complex depends upon the tissue calcium content [17, 18]. Biodistribution studies have proven that in physiological conditions, in tissues with low calcium content (muscles – 0,005% and thyroid gland – 0,03%) the uptake of ^{99m}Tc – diphosphonate complex is just 0,005% ID/gr, whereas in tissues with high calcium content (bone – 14-24%) it can be up to 0,7% ID/gr. The presence of soft tissue calcification can have a substantial effect on changing these parameters, thus increasing the abnormal extra-osseous ^{99m}Tc-MDP accumulation.

Soft tissue calcification can be classified into three major types: metastatic, dystrophic and idiopathic. Dystrophic calcification occurs as a result of tissue damage and is usually associated with normal calcium and phosphate plasma levels. This type of soft tissue calcification includes also some metabolic disorders, amyloidosis, connective tissue disorders – scleroderma, infestations – cysticercosis and different types of vasculitis.

Metastatic calcification, however, is always associated with impaired calcium / phosphate metabolism and previously undamaged soft tissues. It is associated with osteolytic tumors, chronic renal failure – secondary hyperparathyroidism, parathyroid adenoma – primary hyperparathyroidism, vitamin D intoxication or sarcoidosis. The pathogenesis of this process underlines the hydroxyapatite crystal formation with different chemical composition and structure, depending on the etiology and the target organ.

In the literature, many cases of incidental ^{99m}Tc-MDP uptake by the soft tissue have been reported due to various reasons, both benign (tumoralcalcinosis, myositis ossificans) and malignant (sarcomas, adenocarcinomas, metastases) conditions [19, 20, 21]. Mechanisms leading to increased extraosseous / soft tissue ^{99m}Tc-MDP uptake include extracellular / interstitial fluid expansion, enhanced local vascularity and permeability (most frequently during inflammation and processes of tissue reparation), and high tissue calcium concentration. The composition of the calcium deposition and the presence of other elements (e.g. iron and magnesium) are important factors for tracer uptake intensity [22]. The main constituent of visceral organ calcifications is [(Ca Mg)₃(PO₄)₂], while on the other hand, calcifications outside visceral organs have pyrophosphate as one of the main components. The uptake of the radiotracer is higher in the early stages of amorphous deposits

compared with old hydroxyapatite crystals. In general, the earliest stages of calcium deposition are characterized with low calcium/phosphate molar ratio, bigger adsorption capacity, high level of complex hydration and low deposit density. The presence of magnesium ions into the deposits considerably lowers the ^{99m}Tc-MDP adsorption. Iron ions on the other hand, if present in soft tissues, increase the uptake. Considering the above mentioned, the intensity of tracer localization may help evaluate the activity of the soft tissue calcification findings. None of the subjects included into our study had neither impaired function of the parathyroid glands nor chronic kidney failure, so hyperparathyroidism was excluded as a possible cause for metastatic calcification. On the other hand, all pts had osteolytic tumors, 41 of which had positive bone scans for secondary metastases that indicates possible hypercalcemia due to altered calcium / phosphate metabolism. Considering the fact that we found soft tissue calcifications (micro- and macrocalcifications) in 39 patients, and inflammatory and reparative disorders with fibrosis (Hashimoto thyroiditis) and nodular transformation (with capsular and intranodular calcifications) were diagnosed, both of which include tissue dystrophy to some extent, we can suggest possible mixed type of soft tissue thyroid calcification in our subjects (both dystrophic and metastatic). Bone tracer uptake noted in the lower neck on anterior views of bone scans is usually mild and diffusely irregular. This pattern of uptake is most commonly associated with osteoarthritis or seldom metastatic disease of the cervical spine. Lordosis of the lower cervical spine and attenuation of photons from the upper cervical spine by the mandible and submandibular soft tissues also tend to emphasize the normal lower cervical spine uptake [23]. Less commonly, calcification of the laryngeal cartilages and very rarely, free pertechnetate uptake by the thyroid gland, may be responsible for this appearance. However, more pronounced uptake in the neck may indicate specific pathology involving the anterior structures of the neck, most frequently the thyroid cartilage. Ossification of the laryngeal cartilages usually begins after the second or third decade of life, although direct correlation with age is poor. Ossification of the thyroid cartilage has been noted to follow a defined, symmetrical pattern which usually begins at the posterior border near the root of the inferior horn, spreading along the inferior border and reaching the midline where there is usually a separate centre of ossification [24, 25].

In our study, despite in the thyroid gland, we have confirmed by using the SPECT/CT technique that 11 patients had additional MDP uptake due to thyroid cartilage calcifications / ossification, 5 of which had also additional uptake into cervical vertebra, most probably due to degenerative processes.

In the literature, artefacts have also been pointed out to simulate soft tissue abnormal MDP uptake. Although not frequently, during the labelling procedure, there is a possibility of air introduction and ^{99m}Tc-pertechnetate (TcO⁴⁻) formation, which is neither subjected to reduction nor is bound to MDP and remains as a free anion. Biodistribution of free pertechnetate follows the same pattern as iodine and includes accumulation into the thyroid gland, thus simulating soft tissue bone tracer uptake.

In our study, prior to injection, detailed quality control of the radiopharmaceutical was performed, so we excluded the possibility of false positive results for soft tissue tracer uptake. Furthermore, neither gastric mucosa uptake nor salivary glands uptake was noted that could indicate the presence of free pertechnetate.

CONCLUSION

^{99m}Tc-MDP thyroid incidental uptake is not frequent and is possibly caused by the presence of dystrophic or metastatic calcification. Our study underlines the importance of further investigation of incidental findings of bone tracer uptake in the thyroid gland. These findings indicate presence of additional, previously unexpected, active disease processes and contribute in proper patient management and adequate therapeutic approach.

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