Typical and atypical PET/CT findings in non-cancerous conditions

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- Benign disease

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Abstract

Nuclear Medicine multimodality imaging, such as positron emission tomography/computed tomography PET/CT, refers to metabolic tissue characteristics integrated with anatomical details. Fluorine-18-fluorodeoxyglucose (^{18}F-FDG) is the most diffuse radiopharmaceutical and its application is spreading beyond the area of oncology. The causes of high ^{18}F-FDG uptake that were once considered false positives have been identified and the new knowledge about them led to non-cancerous pathologies that can be studied by ^{18}F-FDG PET/CT.

This technique, due to the inflammatory cells high avidity of ^{18}F-FDG, can be useful in studying a variety of inflammatory and infectious systemic conditions.

Studies performed in patients with fever of unknown origin (FUO) indicate that ^{18}F-FDG PET/CT offer a great advantage of detecting malignancy, inflammation and infection at the same time both in adults and children.

Furthermore, the ^{18}F-FDG PET/CT has proved useful in the study of specific organs such as the heart and brain that represent separate topics also for the development of new specific radiopharmaceuticals.

In all the non-oncologic conditions ^{18}F-FDG PET/CT imaging may offer an "all-in-one" procedure, thanks also to its panoramic whole-body acquisition, as an alternative to other diagnostic procedures, reducing the number of unnecessary investigations.

The ^{18}F-FDG PET/CT finding of the simultaneous presence of radiopharmaceutical uptake for multiple disease interconnect to different medical disciplines.

It is important to describe unexpected occasional typical or atypical PET/CT findings to the growth of scientific and medical community; it can be the starting point to the enlargement of PET/CT indications for a better and wider comprehension of the human system.

To recognize unexpected occasional findings is very important a well knowledge of many aspects: physiological biodistribution, diagnostic imaging instrumentations and techniques, pathological aspects of the different neoplastic diseases, patient story, such as previous therapy, and its comorbidity.

An unexpected occasional finding can lead to suggest further tests or investigations in order to have a wider comprehension of patients' clinical situation and they are easily explainable when we have a physician's approach towards patient.

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Introduction

The nuclear biomolecular imaging by positron emission tomography/computed tomography (PET/CT) scans is a powerful tool to investigate human disorders and diseases and it is having a major impact on their diagnosis and treatment. It measures many important body functions, such as blood flow, oxygen use and sugar (glucose) metabolism, in order to evaluate organs and tissues functioning [1].

The association of functional PET data with the morphostructural data provided by CT or MR allows multimodality imaging, which permits to recover also very high specificity, as PET/CT scans have been shown to provide more accurate diagnoses than the two scans performed separately [1].

Indeed, PET/CT scan images allow to correlate and interpret data from two different exams, leading to more precise information and accurate diagnoses. Positron emission tomography/CT scan has many advantages: it has high sensitivity and sensibility, it is a non-invasive method to study body functions and it gives the possibility to have a whole body exploration in one time [2].

Positron emission tomography/CT scan is a validated technique for detecting cancer, staging and restaging of malignant tumors and monitoring therapy response. Otherwise, PET/CT scan can also be used to study and diagnose non-cancerous conditions, as it shows how organs are functioning because it investigates the activity within the body

on a cellular level [3].

Fluorine-18-FDG PET/CT

In recent past the detection of benign lesions on ^{18}F-FDG PET/CT for cancer staging was considered a "minus" representing possible false positive findings to correct diagnosis. Currently the detection of benign lesion is a proper indication for PET/CT studies. Description of typical and atypical PET/CT findings in non-cancerous conditions is a very important topic for the diagnostic imaging community [3].

The description of benign lesions detectability on PET/CT is becoming wider and also literature data are growing. Literature about this topic, researchable on official sites such as PubMed, is mainly consisting of case reports, giving everyone the opportunity to study, evaluate and share the real efficacy of this exam in conditions different from the usual cancerous ones. This will permit to enlarge the possible indications of this technique, also modifying the official list of diseases in which the different PET radiopharmaceuticals can be used [3].

Nuclear Medicine Imaging is characterized by a strict relation between radiopharmaceuticals and tissue metabolic pathways. The radiopharmaceutical distributes differently in organs and tissues according to the metabolic level activity of each district. The images resulting from this type of study allow an accurate description of the activity of the entire body and this is the reason why PET/CT is considered to be a well validated whole body technique based on biometabolic aspects of normal and pathological cells [4].

Positron emission tomography/CT non cancerous findings may be classified according to two criteria: distribution pattern, as the finding may be typical or atypical; numeric, as the finding may be single or multiple. The correct analysis and interpretation of the whole body PET/CT images requires various knowledge, such as the physiological biodistribution of elements and radiopharmaceutical, the functioning of diagnostic imaging instrumentations and the various techniques, the pathological aspects of the different neoplastic diseases and the patient clinical history and his comorbidity. Only having all the elements together it is possible to give a correct interpretation of the PET/CT images [3].

Fluorine-18-FDG physiologically concentrates in all the sites with elevate glucose metabolism, such as brain, myocardium, liver and in the urinary excretory system.

Other organs may be sites where ^{18}F-FDG concentrates in particular conditions; for example, brown fat tissue when temperature is particularly cold and muscles in case of uncontrolled diabetes.

The ^{18}F-FDG uptake is considered pathological, but not associated to a cancerous condition, when diseases with high metabolism and glycolysis occur [3].

The most common diseases are:

- inflammatory diseases, as osteomyelitis and spondylodi citis;
- bone disorders, as osteopetrosis;
- granulomatous diseases, as the Erdheim-Chester disease;
- reumatologic diseases, as rheumatoid arthritis, rheumatic polymyalgia and lupus erythematosus;
- FUO;
- infectious diseases.

Osteomyelitis is an inflammatory condition characterized by a high glucose metabolism and for this reason it can be studied well by PET/CT scan. It is a bone infection that can be caused by many factors, like bloodstream, nearby areas or injuries. Symptoms are often non-specific, including fever, swelling, warmth and redness, local pain and fatigue; these features are in common with many other diseases because they are the general symptoms of inflammation. So to be able to do a correct diagnosis of osteomyelitis it is necessary to perform other exams, such as X-rays, CT or magnetic resonance imaging (MRI), which remains the gold standard nowadays [5].

The ^{18}F-FDG scan can be helpful in diagnosing osteomyelitis (Figure 1) and it has many advantages in comparison to MRI, such as no age limitation, and it can be performed when there are metallic implants in situ, condition that contraindicates MRI. Furthermore, it has excellent sensitivity (95%) and good specificity (87%); it allows to diagnose periprosthetic infections, that may not be seen by MRI in early stages, and to differentiate septic and aseptic prosthetic loosening (Figure 2), visualizing the typical hypermetabolic inflammation sites also in the contiguous soft tissues (Figure 3) [6].

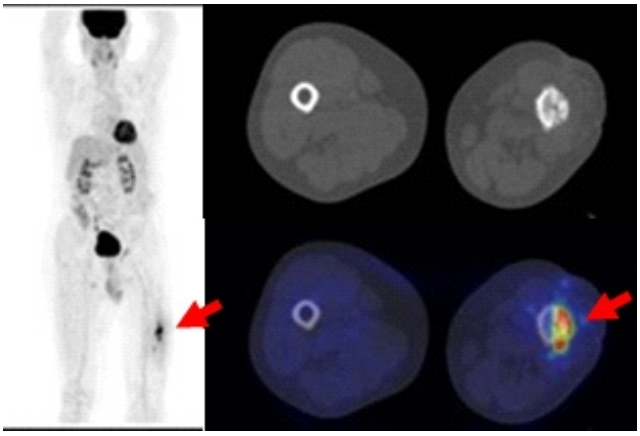

Figure 1. A 59 year old man with left femur fracture treated with surgery and complicated by osteomyelitis unresponsive to antibiotics. Fluorine-18-FDG PET/CT: typical hypermetabolic lesion in the left femur and contiguous soft tissues.

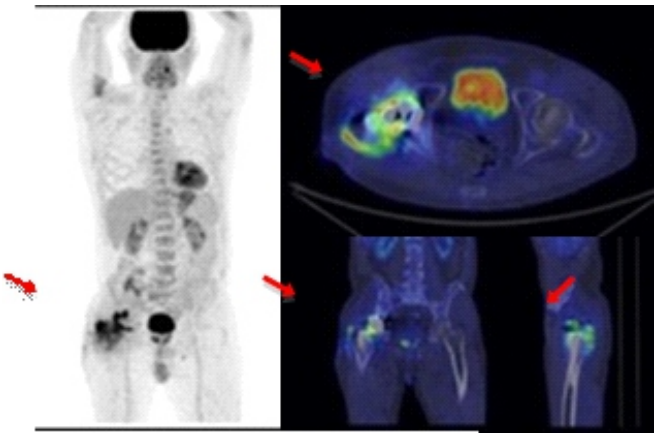

Figure 2. Previous implant of right hip prosthesis. Recent appearance of fistula on intervention's site. Fluorine-18-FDG PET/CT: typical pathological uptake in the periprosthetic soft tissues of the right hip.

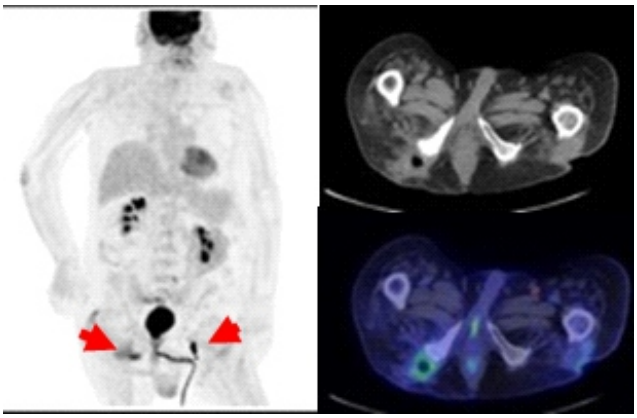

Figure 3. Tetraplegic 53 year old patient with recent onset of right gluteus weal. Computed tomography: fistula in the right gluteal region and signs of osteomyelitis. Fluorine-18-FDG PET/CT: typical ^{18}F-FDG uptake in peri-articular soft tissues of the right coxo-femoral joint in the right gluteal region and in inguinal lymph nodes.

Spondylodiscitis is the inflammation of one (or more) intervertebral disc associated with the inflammation of one (or more) vertebrae and it can complicate with local infection or sepsis. It is a common disease in immunocompromised patients because of the reduction of the immunological system functioning. The diagnosis is made by blood culture or tissue biopsy and MRI [7].

Fluorine-18-FDG plays a role in spondylodiscitis study, as it can be useful not only to confirm the diagnosis but also to evaluate the response to treatment (Figure 4). The comparison between pre-treatment PET/CT scan and post-treatment one can give a practice and numerical data of the ^{18}F-FDG uptake; the decreased uptake means good response to specific antibiotic therapy. Moreover, ^{18}F-FDG can also reveal extravertebral involvement, like epidural abscess and muscular involvement (Figure 5), which are the most common complications that may be unrecognized by MRI [7].

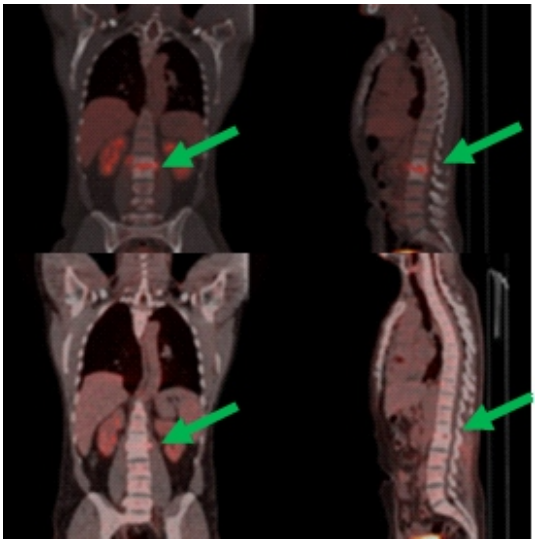

Figure 4. A 38 year old with lumbar region pain and fever. MRI: spondylodiscitis of L1-L2. Vertebral biopsy: infectious spondylodiscitis (S. Epidermidis). Pre-treatment ^{18}F-FDG PET/CT: increased uptake of L1-L2 (SUV max 9.8) and near soft tissue involvement. Post-treatment ^{18}F-FDG PET/CT: decreased ^{18}F-FDG uptake of L1-L2 (SUV max 3.1) that means good response in antibiotic therapy.

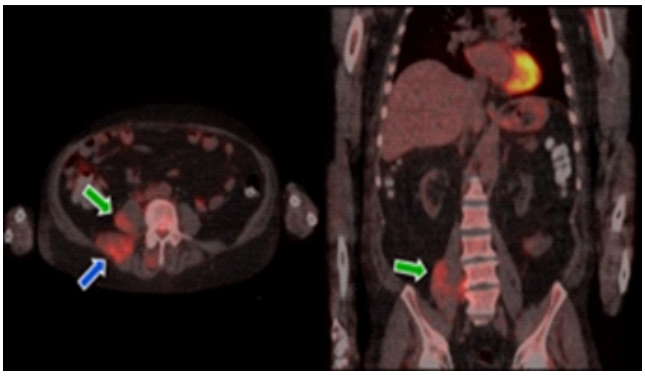

Figure 5. Patient with spondilodiscitis of L4-L5 and epidural abscess at MRI. Fluorine-18-FDG PET/CT: typical ^{18}F-FDG uptake in L4-L5 due to spondiylodiscitis and unexpected uptake in longissimus muscle and in psoas major muscle as complication (green arrows).

Osteopetrosis, also known as marble bone disease, is an extremely rare inherited disorder causing osteosclerosis whereby bones become denser and harder until they may even dissolve and break. It can result in deformity, blindness and paralysis, craniosynostosis and abnormal bone morphology [8].

Patients may suffer anemia, recurrent infections and hepatosplenomegaly if the disease is particularly serious, due to bone expansion leading to bone marrow. Sometimes X-rays and MRI may unrecognize osteopetrosis imaging and they may reveal imaging alterations suspicious for other diseases, such as cancer or Paget's disease. Fluorine-18-FDG PET/CT scan, otherwise, can be useful (Figure 6), in particular when the glucose uptake is unexpected and atypical and involves the surrounding soft tissues [8-9].

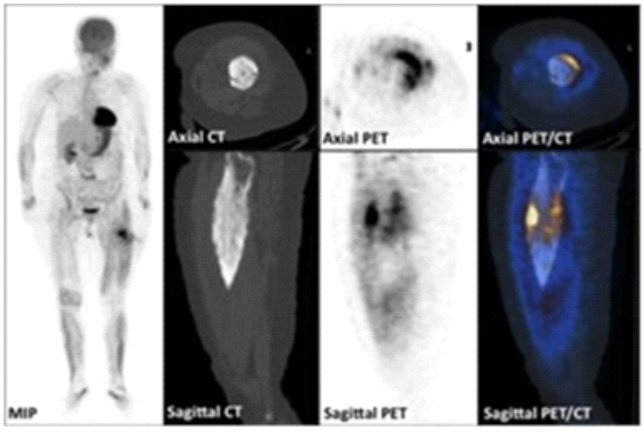

Figure 6. A 63 year old woman with persistent low limbs pain. Fluorine-18-FDG PET/CT: unexpected and atypical pathological uptake in the left femour (SUV max 8.7) and mild uptake in the surrounding soft tissues (suspect for osteosarcoma) (guiding biopsy). Biopsy on the lesion detected by ^{18}F-FDG PET/CT: osteopetrosis [8].

Erdheim-Chester disease (ECD) is a granulomatous disease and can be studied by ^{18}F-FDG PET/CT scan. It is a rare form of non-Langerhans' cell histiocytosis characterized by systemic granulomatous infiltrative disease with unknown etiology. More than half of cases have extraskeletal involvement, including kidney, sin, brain, lung and pituitary gland [10].

The most common symptom is bone pain, described as mild but permanent, in association with arthro myalgia, fever, anorexia, polydipsia, nocturnal and diurnal polyuria, symptoms suggestive of insipidus diabetes, which is often concomitant. The diagnosis is radiological, as the main feature is the osteosclerosis, and it is confirmed by histology [10].

Fluorine-18-FDG PET/CT is useful because it gives whole-body and brain images of this particular disease: as expected, the glucose uptake is generally high in the pituitary gland and a typical diffuse bone narrow glucose uptake is visible bilaterally and symmetrically, for example in the proximal and distal epiphysis and proximal metaphysis of homer and femour, but also in shoulder and pelvis bones [11].

Fluorine-18-FDG PET/CT scan is particularly useful and is playing a growing role in rheumatologic diseases, such as rheumatoid arthritis, rheumatic polymyalgia and lupus erythematosus [12].

Rheumatoid arthritis is a long term autoimmune disorder characterized by synovial infiltration of metabolically active immune cells that affects joints primarily, most commonly wrists and hands. Its diagnosis is made with blood tests and may be supported by X-rays or MRI imaging, following the ACR/EULAR criteria. Fluorine-18-FDG PET/CT role is interesting because it can detect articular and extra-articular inflammation sites that may be undetected by other exams and it can estimate the disease activity level thanks to the SUVmax data; the higher is SUVmax the more intense is the disease activity. Positron emission tomography/CT is fundamental also in the treatment and follow up steps; it allows to evaluate early treatment response, by the comparison of a following PET/CT scan with the first "baseline" one, showing the progressive decrease glucose uptake in the affected joints, and it is predictive of the outcome in advanced state patients [12-13].

Rheumatic polymyalgia is an inflammatory disorder that causes muscle pain and stiffness, especially in the shoulders. It can be associated with giant cell arteritis. Fluorine-18-FDG PET/CT is as useful for this disease as it is for rheumatoid arthritis; it has a role in the diagnosis of the disease and it can be useful in the evaluation of the treatment response (Figure 7), as it shows how the typical glucose uptake in the shoulders, the spinous processes of the lower lumbar vertebrae and the ischial tuberosity is normalized after therapy [14].

Among rheumatic diseases, systemic lupus erythematosus (SLE) is an immune complex disease of unknown etiology, which causes excessive production of autoantibodies to components of the cell nucleus. In few cases, SLE can result in an uncommon and unexpected diffuse lymphadenopathy throughout the whole body and ^{18}F-FDG PET/CT helps in visualizing the increased glucose uptake in lymph nodes affected by SLE, potentially mimic of lymphoma [15].

Another disease that can be helpfully studied by PET/CT is Fever of Unknown Origin (FUO). The definition of FUO is difficult and in constant refreshment because of the advancement of imaging techniques and biomarker analysis. It is possible to talk about FUO when body temperature exceeds 38.3°C at least 3 times over a period of at least three weeks in absence of diagnosis despite one week of investigations [16].

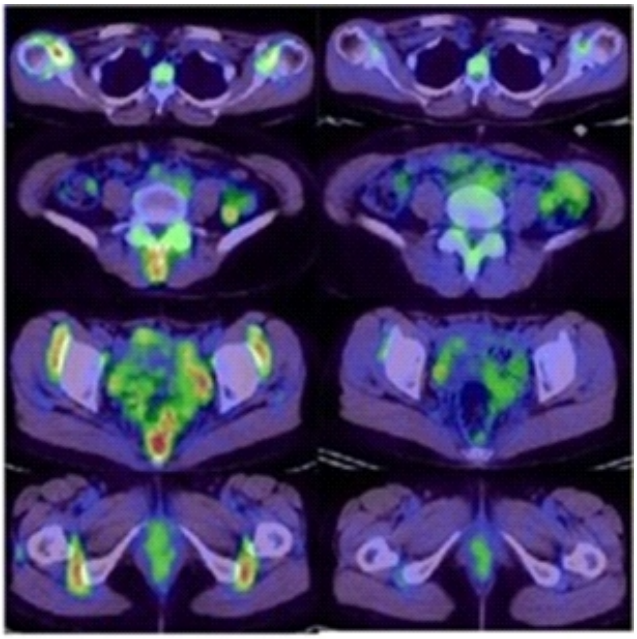

Figure 7. Fluorine-18-FDG PET/CT at diagnosis and after steroid treatment. Typical ^{18}F-FDG uptake in the shoulders, spinous processes of the lower lumbar vertebrae, iliopectineal bursitis, and ischial tuberosity is normalized after therapy [14].

Fluorine-18-FDG PET/CT role in the study of this disease is the possibility to detect malignancy, inflammation and infection at the same time both in adults and children and to make early diagnosis of occult sources of infection in immunocompromised patients (opportunistic infections). As a matter of fact, it is recommended in patients with high-risk Gram-positive bacteremia or suspected disseminated infection (Figure 8) [17-18].

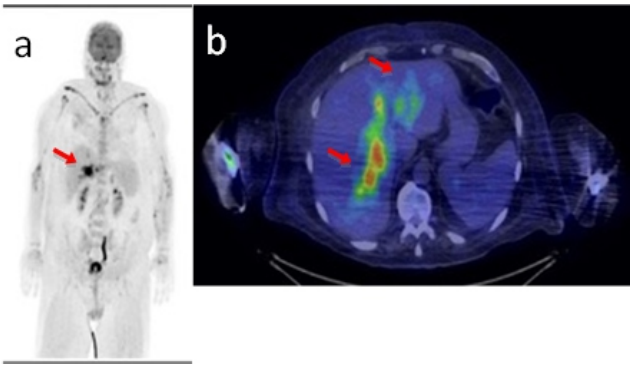

Figure 8. Male, 59 year old with FUO and asthenia. Hepatic biopsy without guide: fibrosis and chronic inflammation, signs of hepatitis. MRI: hepatic interstitial thickening. Fluorine-18-FDG PET/CT: unexpected focal lesions in the VIII-V and II hepatic segments, in the laterocervical and mesenteric lymph-nodes, clavicles, humeri and in the sternum. Second liver biopsy PET guided: address to correct diagnosis of hepatic lymphoma.

Sometimes cancerous conditions are accompanied by infectious ones that may be undetected because of the predominance of the neoplasm. For example, lung carcinoma might be associated to pneumonia misread in the traditional imaging; PET/CT reveals the infections because it can evaluate the high unexpected glucose uptake nearby the cancer (Figure 9) [19-21]. Fluorine-18-FDG PET/CT plays a role also

in the evaluation of the treatment response in alter-native to other imaging exams. For example, post-treatment MRI images may be a false positive because an apparent reduction of edema in the soft tissues may be considered suggestive of response to treatment; otherwise ^{18}F-FDG PET/CT studies the glucose uptake and it can reveal an eventual progression of the disease, apparently undetected by MRI, so it has a role in the decision of the establishing a new therapy [19, 22].

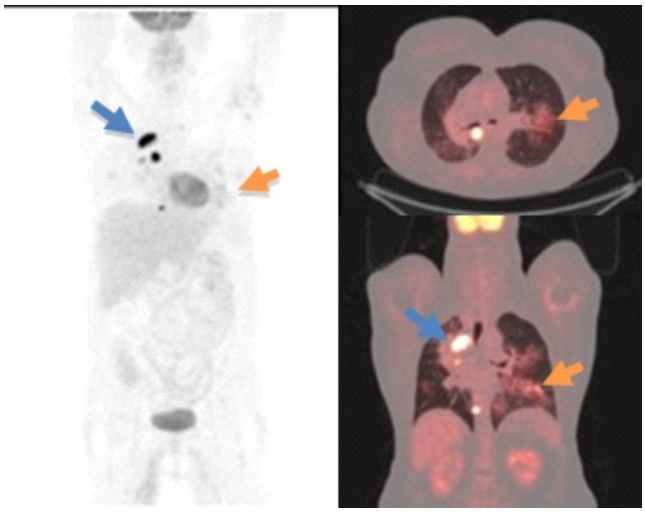

Figure 9. A 59 year old woman with right lung carcinoma. Fluorine-18-FDG PET/CT: expected and typical pathological neoplasmatic uptake (blue arrow); unexpected and atypical presence of diffuse ^{18}F-FDG uptake in the right lung lobe (green arrow) due to infection. Final diagnosis: lung carcinoma and simultaneous aspergillosis.

Tubercolosis is another infectious disease which can be studied by PET/CT. It is caused by Mycobacterium Tubercolosisand it is a granulomatous inflammatory disease with pulmonary localization in 90% of the cases and extrapulmonary localization in the remnant 10% of the cases; it can involve pleura, central nervous system (CNS), lymphatic system, genitourinary system, bones and joints. Its presentation can be classified as disseminated or as military, depending on the number and the dimensions of the lesions [23].

Its diagnosis bases on the presence of typical symptoms, according to the district affected by the disease, and it is confirmed by instrumental exams, such as chest X-rays, culture or PCR. Fluorine-18-FDG PET/CT allows to obtain a whole body evaluation, revealing also extrapulmonary localizations, and gives an evaluation of early therapeutic response. Moreover, it is useful for making differential diagnosis between active granulomatous inflammation and fibrous lesions, in order to study the activity level of the disease [23].

Sarcoidosis is defined as a chronic multisystemic inflammatory disease of unknown origin characterized by the widespread appearance of granulomas derived from the reticuloendothelial system. It has a highly variable and non-specific clinical presentation so the diagnosis is particularly difficult; organs most commonly involved are lungs, lung hilar lymph nodes, reticuloendothelial system and bone marrow, while organs less commonly involved are eyes, skin, liver, heart and CNS. Standard blood chemistry tests, including ACE, together with chest X-rays and chest CT are routinely performed in order to make an diagnosis, but they don't allow to obtain a definitive one anyway. Patients affected by sarcoidosis undergo and perform ^{18}F-FDG PET/CT scan in addition to traditional exams and it is useful because in this way it is possible to detect unexpected organ involvement and to obtain morphofunctional assessment of the inflammatory active localizations (Figure 10). Furthermore, the changes in time of the glucose uptake are indicative of treatment efficacy, in particular in atypical, complex and multisystemic forms, and this gives PET/CT a role in the follow up of the disease [24-25].

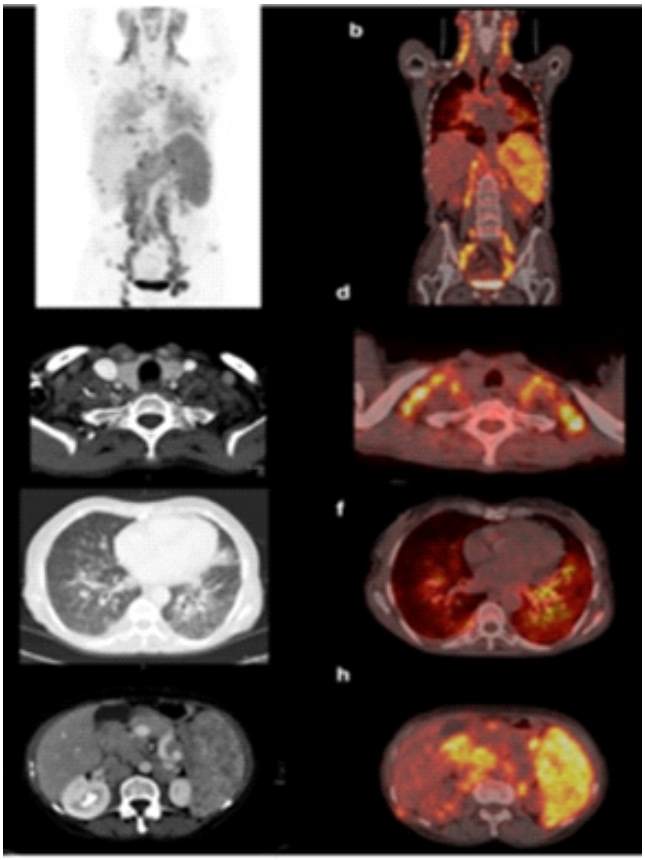

Figure 10. Patient with systemic sarcoidosis diagnosed by biopsy of the laterocervical lymph nodes. Whole body ^{18}F-FDG PET/CT: typical but systemic sarcoidosis with multiple lesions of the supraclavicular and thoracic lymph nodes, lungs, abdominal lymph nodes, liver and spleen [24].

Idiopathic retroperitoneal fibrosis (RPF) is a rare fibro-inflammatory disease characterized by a highly fibrotic retroperitoneal mass developing around the abdominal aorta and the iliac arteries. In some cases the mass can spread into the adjacent retroperitoneum causing frequently other organs involvement, such as ureteral obstruction and renal failure. ^{18}F-FDG PET/CT can study this disease evaluating the activity level of fibrosis and identifying extraperitoneal or secondary lesions undetected by traditional imaging; it can also give an assessment of RPF activity. It is useful to establish an eventual post-treatment residual disease, addressing therapy's choice (Figure 11). Other fibro-inflammatory diseases that may be evaluated by ^{18}F-FDG PET/CT are fibrosing mediastinitis and mesenteric panniculitis [26-27].

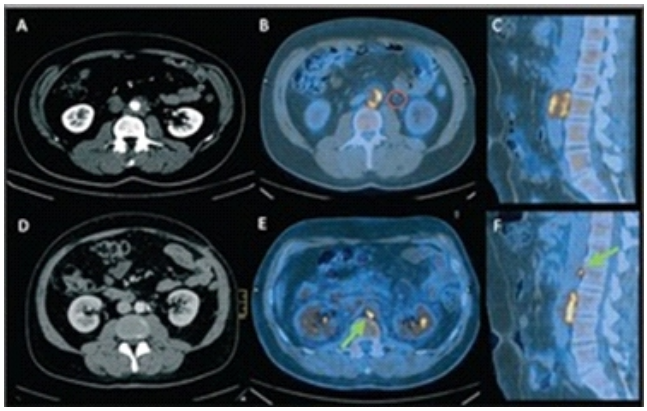

Figure 11. A 43 year old man with cramp-like abdominal pain and presence of periaortic solid tissue in the infrarenal section and locoregional lymph nodes interpreted as lymphomatous tissues. Baseline ^{18}F-FDG-PET/CT: uncommon uptake in solid periaortic tissue and locoregional lymph node. Laparoscopic biopsy PET/CT guided suggestive for IRF and following corticosteroid therapy. Post corticosteroid therapy ^{18}F-FDG-PET/CT: size reduction of the solid tissue [27].

Vasculitis is a generic term to define a multisystem inflammatory disease that can affect any type of blood vessel in any organ. The clinical presentation is various, depending on vessels type involved, and it can reveal from isolated benign and self-limiting cutaneous vasculitis to life threatening widespread internal organ involvement. Fluorine-18-FDG PET/CT performed in patients with vasculitis gives a whole body evaluation of each involved vessel, mostly large-vessels, and it allows to make early diagnosis; it evaluates the disease activity level and it identifies high risk patients according to the glucose uptake level and the number and the localization of the vessels involved (Figure 12). Positron emission tomography/CT can be useful to make differential diagnosis with atherosclerosis: the glucose uptake is linear along the vessels' walls affected by vasculitis, while it is discontinuous in atherosclerotic vessels, where hot spots are visible [28-30].

Figure 12. A 72 year old woman with fever, asthenia, headache and weight loss. Whole body CT: pulmonary nodule. ^{18}F-FDG PET/CT: unexpected and occasional findings FDG linear uptake of aortic and large-vessel walls permit the correct diagnosis.

Atherosclerosis is a arteries' disease characterized by the presence of plaques deforming the vessels' walls and the blood flow. These plaques become instable in time and when they arrive to a vulnerable situation they can break modifying the blood flow's homeostasis. In particular, carotid plaques are the primary cause of acute cerebrovascular events. Fluorine-18-FDG PET/CT represents a morphofunctional technique able to identify the highly inflamed and most vulnerable carotid plaques in early stages; it can be useful as biomarker of disease activity and in the identification of patients with high cardiovascular risk. As described before, PET/CT images reveal a typical focal and discontinuous glucose uptake along arterial walls, described as hot spots, suggestive of active plaques (Figure 13) [31].

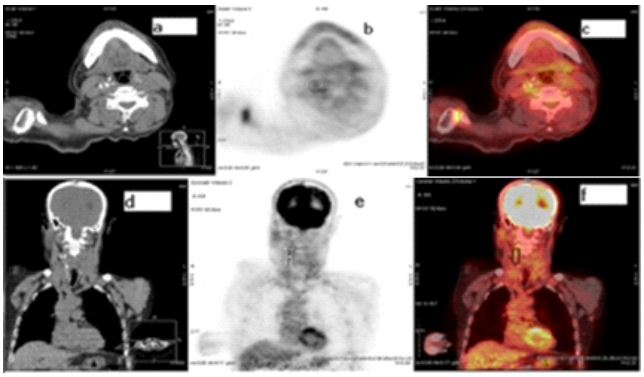

Figure 13. Fluorine-18-FDG-PET/TC: typical focal ^{18}F-FDG uptake in right carotid vessel, suggestive of active carotid plaque [31].

Sometimes one single patient may be affected by different pathological conditions or diseases. Fluorine-18-FDG PET/CT investigation is really useful in these cases as it can reveal undetected secondary localization of neoplasm, unsuspected septic processes or unknown inflammatory consequences (Figure 14) [32].

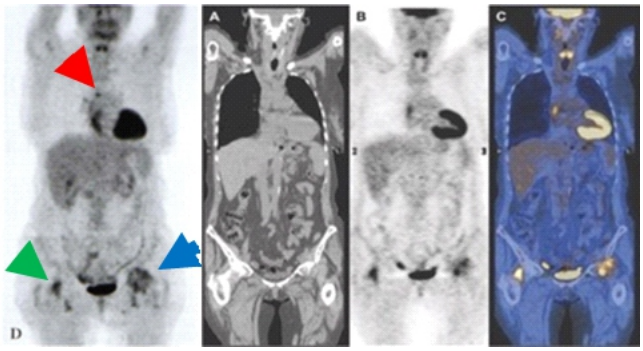

Figure 14. A 64 year old woman with Non Hodgkin Lymphoma diagnosis, immunosuppression after chemotherapy and joint pain at the left hip joint. body ^{18}F-FDG PET/CT shows: typical and expected lymphnodal uptake (SUV max 6.1) due to NHL recurrence; typical and expected uptake at left hip joint (SUV max 6.4) raised the suspicion of a septic process; unexpected uptake in the right hip muscular insertions (SUV max 6.5).

Thyroid is an organ that may be affected by different diseases whom evaluation ^{18}F-FDG PET/CT may be useful for. Thyroid adenoma is a benign tumor of the thyroid gland, that may be inactive or active; when it is functionally autonomous as a toxic adenoma it can cause hyperthyroidism. When the whole thyroid gland is enlarged and it contains multiple nodules, functionally inactive or active, it is possible to define it as a multinodular goiter; when the nodules are active, the goiter is toxic and it is associated with hyperthyroidism. Increased glucose uptake in the thyroid site is often an occasi-

onal finding when performing ^{18}F-FDG PET/CT for other reasons (Figure 15). Positron emission tomography/CT may result useful as it can distinguish benign and malignant lesion: diffuse uptake is more likely related to a benign condition, while focal uptake should be investigated to exclude malignancy [33].

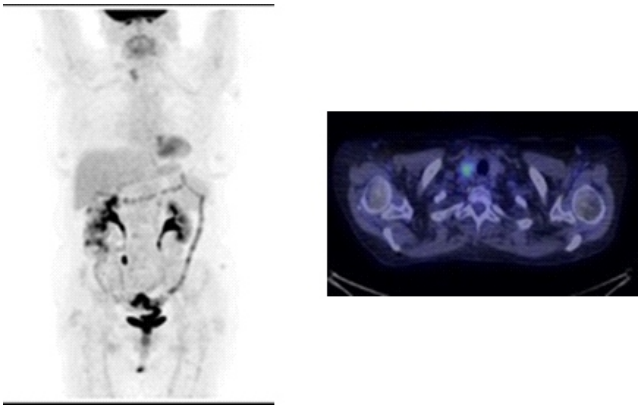

Figure 15. Female, 60 year old, evaluated for a nodule in the left lung. Fluorine-18-FDG PET/CT: occasional typical uptake in a nodular lesion in right thyroid lobe (arrow) due to toxic adenoma.

A similar situation may be found during the study of the suprarenal glands; adrenal adenoma is a benign tumor of the adrenal cortex. Clinically it can be silent as non functioning; in this cases its finding is occasional and it is defined as an incidentaloma. Otherwise, if functioning, adrenal adenoma can reveal in Cushing syndrome or Conn's syndrome or hyperandrogenism. Fluorine-18-FDG PET/CT normally identify adrenal adenomas as masses with a low glucose metabolism; in 3% of cases they show a more intense uptake (Figure 16). In some cases increased uptake can be related to hormone secretion [34].

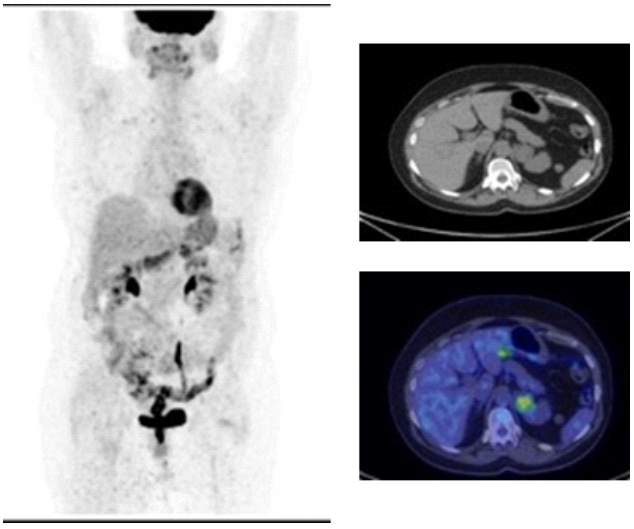

Figure 16. A 58 year old woman. Abdominal CT: left adrenal incidentaloma. Fluorine-18-FDG PET/CT: occasional typical uptake in the left adrenal gland.

The group of inflammatory conditions of the colon and the small intestine, defined as bowel inflammatory disease, may be occasionally found during PET/CT executions; Chron's disease and ulcerative colitis are the principal types and they are suspected when glucose uptake is higher in bowel (Figure 17) [35].

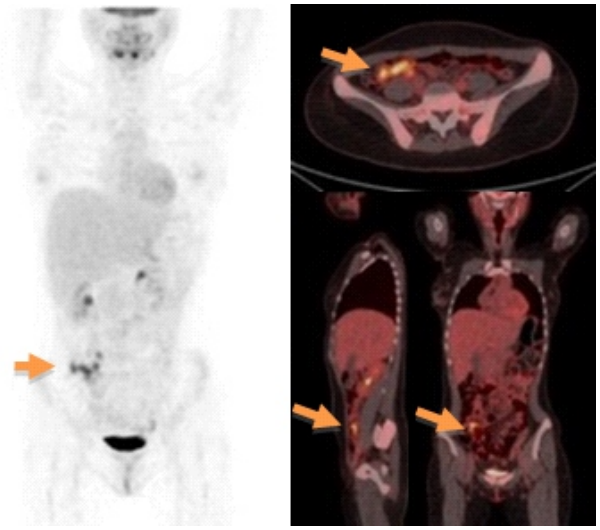

Figure 17. A 19 year old woman evaluated for axillary lymphadenomegaly with recent diagnosis Chron's disease. Fluorine-18-FDG PET/CT: expected and typical uptake in bowel (green arrow), relate to IBD.

Hemangioma is a benign tumor derived from blood vessel cell types that can occur anywhere in the body; skeletal localizations are commonly benign conditions which are typically ametabolic on ^{18}F-FDG PET/CT images (Figure 18) [36].

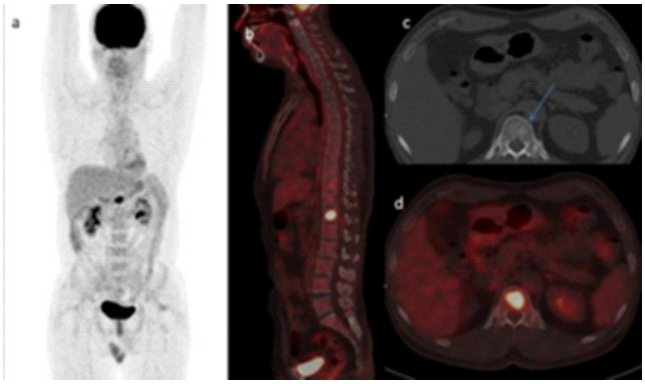

Figure 18. A 54 year old man with suspicion of tonsillar carcinoma. Fluorine-18-FDG PET/CT: unexpected and atypical uptake in T12 vertebra (SUVmax 7.2). Following MRI diagnosed vertebral hemangioma [36].

Many benign conditions can cause an increasing breast glucose uptake on PET/CT, such as pregnancy and lactation, gynecomastia, mastitis, fat necrosis, fibroadenoma, intraductal papilloma and atypical ductal hyperplasia. The uptake can be focal or diffuse, monolateral or bilateral, depending on the type of lesion, its metabolism and its activity level [37].

Gynecological conditions can be revealed by ^{18}F-FDG PET/CT; frequently in patients with squamous cell carcinoma of the cervix and a metallic localizer placed in the vaginal vault for radiation therapy purposes, uncommon and unexpected vaginal uptake is visible. This could be misinterpreted as a local recurrence, but corrected PET/CT images can help in showing any trace of uptake activity, leading to a correct diagnosis and avoiding medical error (Figure 19) [38].

Physiologic and typical endometrial uptake can be studied in fertile women during the menstrual flow phase; normal ovulation can be observed by PET/CT and sometimes the comparison between the two sides can reveal ovarian complex masses suspicious for ovarian cystadenocarcinoma (Figures 20, 21, 22) [39].

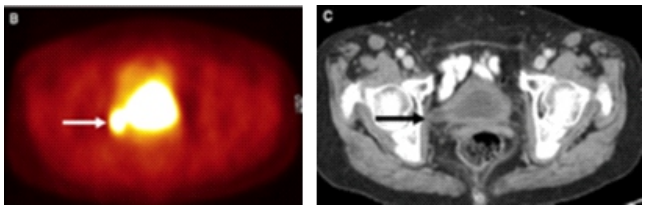

Figure 19. Unexpected but typical bladder diverticulum [39].

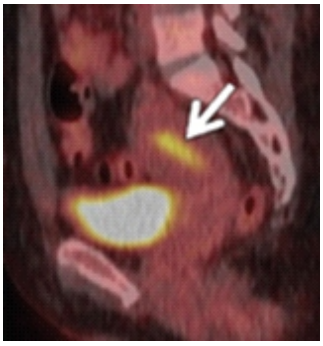

Figure 20. Physiologic and typical endometrial uptake in a 34 year old woman during the menstrual flow phase [38].

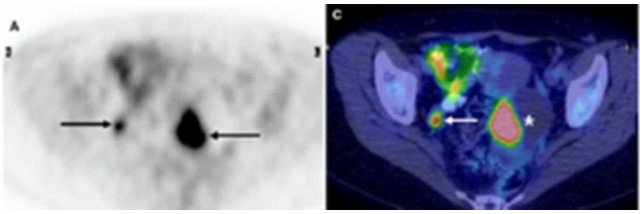

Figure 21. Ovulating 41 year old patient with a left ovarian complex mass suspicious for ovarian cystadenocarcinoma and (typical) right normal ovulation [39].

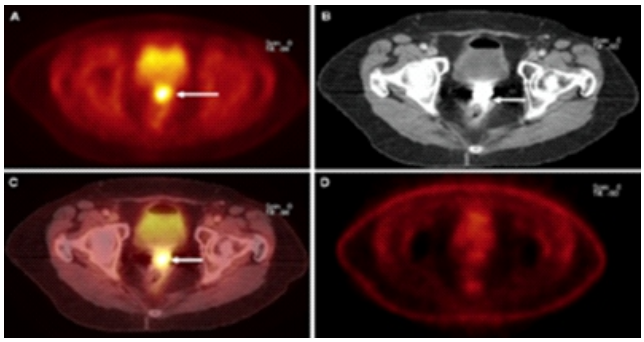

Figure 22. Patient with squamous cell carcinoma of the cervix and a metallic localizer (for radiation therapy purposes) placed in the vaginal vault. The uncommon and unexpected vaginal uptake could be misinterpreted as a local recurrence if attenuation-corrected PET/CT images were taken into account. Non-attenuation corrected PET image correctly (D) does not show any trace of uptake activity [39].

Brown adipose tissue (BAT) is a thermogenic organ present especially in young patients; glucose uptake become more intense in BAT and it can be confused with nodal uptake. Brown adipose tissue can occasionally be revealed by ^{18}F-FDG PET/CT as a physiological occasional finding due to metabolic changes that occur when temperature goes down (Figures 23, 24) [40].

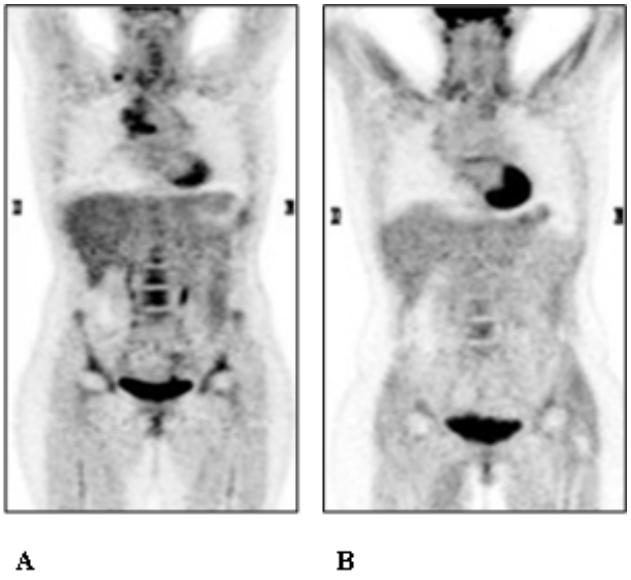

Figure 23. A 29 year old woman with Hodgkin Lymphoma diagnosis. A: staging ^{18}F-FDG PET/CT: pathological ^{18}F-FDG uptake in right supraclavicular, bilateral paratracheal and mediastinal lymph nodes; typical and unexpected ^{18}F-FDG uptake in supraclavicular and paravertebral regions due to BAT activation (external temperature 12°C). B: follow up ^{18}F-FDG PET/CT: ^{18}F-FDG uptake in laterocervical region due to BAT activation (external temperature 5°C).

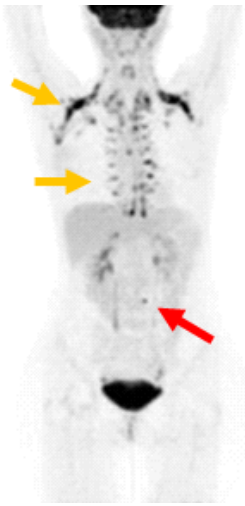

Figure 24. A 38 year old woman with breast cancer. Staging ^{18}F-FDG PET/CT shows L3 pathological uptake; the ^{18}F-FDG uptake in bilateral laterocervical, supraclavicular, axillary and paravertebral regions is due to diffuse BAT activation.

Fluorine-18-FDG PET/CT performed in diabetic patients can detect an increased glucose uptake in skeletal muscles, myocardium and bowel, because of hyperglycemia. It is a physyological finding because the radiopharmaceutical distribution depends on glucose blood level. If we perform a ^{18}F-FDG PET/CT in euglicemy, the upper described high uptake sites will be no more visualized (Figures 25, 26) [41].

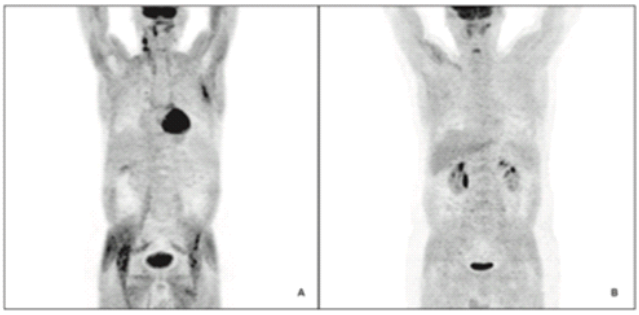

Figure 25. A: Fluorine-18-FDG PET/CT performed during follow-up in a patient with lung cancer showed typical but unexpected increased uptake in the myocardium and muscles because of acute hyperglycemia (blood glucose >11.1mmol/L). B: Fluorine-18-FDG PET/CT performed 8 months later and in euglycemy showed best quality images [41].

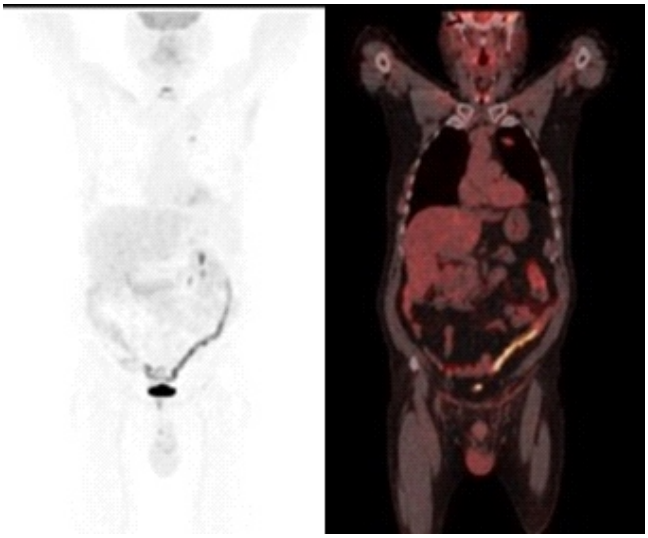

Figure 26. A 62 year old patient with lung cancer and type 2 diabetes treated with metformin. Fluorine-18-FDG PET/CT showed typical aspecific increased uptake in bowel due to diabetes.

Fluorine-18-FDG PET/CT plays an important role in the evaluation of treatment's side effects; new oncologic therapies, such as immunotherapy, can give side effects due to the activation of lymphocytes that correspond to sites of glucose uptake (Figure 27). For example, hepatomegaly and splenomegaly are frequent findings in ^{18}F-FDG PET/CT of patients with melanoma who undergo immunotherapy (Figure 28); the glucose uptake in these sites is typical and expected because of the lymphatic system activation. Radiotherapy has side effects, too; it induces fibrous healing reactions with surrounding inflammation in the sites of irradiation. For example, radiotherapy performed in patients with head and neck cancer can induce mandibular osteonecrosis such as radiotherapy performed in patients with lung cancer leads to lung fibrosis (Figure 29) [42].

Non-^{18}F-FDG PET/CT Radiopharmaceutical

Both the type of the images and the goals that want to be obtained by PET/CT investigation depend on the type of radiopharmaceutical administered. Radiopharmaceuticals have specific clinical and diagnostic indications and are used according to what has to be studied as every radiopharmaceutical evidences a different metabolic pathway. Fluorine-18-FDG investigates the glucose metabolism and it is the most used radiopharmaceutical [43].

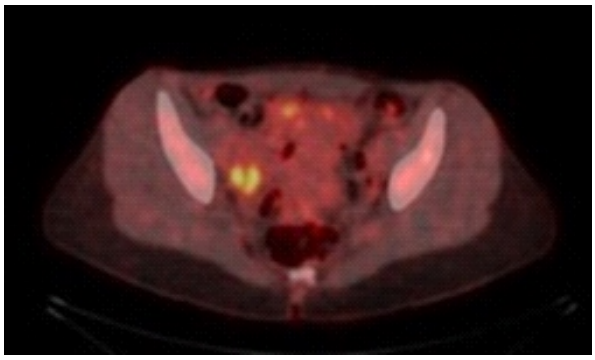

Figure 27. Typical colitis after immunotherapy in a patient with lung cancer.

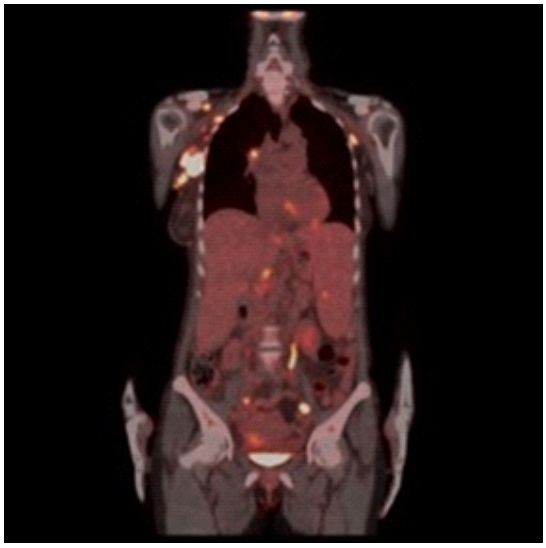

Figure 28. Typical and expected hepatosplenomegaly after immunotherapy in a patient with melanoma.

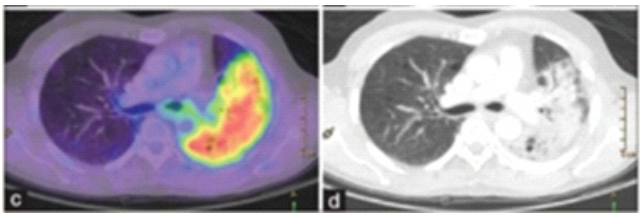

Figure 29. Typical and expected radio-induced lung fibrosis [42].

Many other radiopharmaceuticals are used in more specific conditions as they allow to study specific pathways; for example, Choline follows the phospholipidic metabolism, tyrosine the aminoacidic one and ^{18}F-sodium fluoride (NaF) the calcium one; Dopamine and DOTA-peptides are ligands of dopamine and somatostatine receptors respectively; prostate specific membrane antigen (PSMA) targets only PSMA-expressing cells; moreover even infective probes, such as gallium-68 (^{68}Ga)-Ciprofloxacine conjugates, ^{18}F-fluorodeoxysorbitol and carbon-11 para-aminobenzoic acid (^{11}C-PABA), are useful as they studies specific bacterial metabolisms or are directed to receptors expressed on the bacterial surface [1].

Each radiopharmaceutical has its own normal biodistribution, which has to be known in order to evaluate the pathological (benign or malign) uptake during the performed PET/CT scans [1].

Fluorine-18-Choline is a radiopharmaceutical used in Nuclear Medicine in alternative to ^{18}F-FDG because it studies a different metabolic pattern, as choline follows the phospholipidic metabolism. In particular, its principal use is the evaluation of a benign hepatic affection, the focal nodular hepatic hyperplasia.

It is the most frequent benign solid hepatic tumor and, after hemangioma, the second most common benign lesion. It is caused by arterial abnormality, often a malformation, causing hypo- or hyper- perfusion of a liver segment or area. In 80% of cases the disease is asymptomatic and may remain unrevealed for a long time until it is detected as an occasional finding. The presence of focal nodular hepatic hyperplasia can be evaluated with ^{18}F-fluorocholine (FCH) PET/CT showing an expected increased uptake in the nodular area. It is interesting to evaluate patients' treatment response after specific therapy; post-therapy ^{18}F-FCH PET/CT shows the expected decreased uptake in the involved area as demonstration of the treatment result (Figure 30) [44].

Gallium-68 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (^{68}Ga-DOTA)-peptides is another group of radiopharmaceutical available in Nuclear Medicine begin ligands of somatostatine receptors (SSTR). Their uptake may result increased for many reasons, such as prominent pancreatic uncinate process activity, inflammation, increased osteoblastic activity and splenosis. In addition, they allow to detect benign and malignant thyroid tumors, that have been observed to express SSTR. For example, patients with an incidental focal abnormal thyroid uptake on ^{68}Ga DOTATATE PET/CT scan are asked to have further clinical evaluation to address correct diagnosis (e.g. thyroid cancer, MEN), as PET/CT has not a diagnostic value [45].

Gallium-68-PSMA finds its targets on PMSA-expressing cells. Commonly it is used as radiopharmaceutical to detect the typical PMSA uptake related to antiandrogen therapy in patients with prostate cancer (Figure 31). There may be interpretative pitfalls caused by many situations, for example focal prostatitis or areas of benign prostatic hyperplasia, reactive lymph nodes, lung infection/pneumonia, atelectasis and inflammation related to pleural plaques (asbestos), atherosclerotic arteries, Paget disease, sites of healing fractures, degenerative arthritis in the spine or peripheral joints, polycythemia rubra vera and fistula [46].

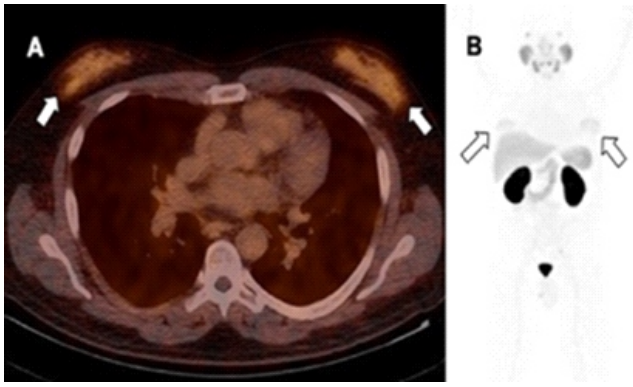

Figure 31. Gallium-68 PSMA PET/CT in a gynecomastia demonstrates increased PSMA uptake, related to antiandrogen therapy for prostate cancer [46].

Fluorine-18-NaF is a radiopharmaceutical that follows the calcium metabolism. It is used to study and evaluate skeleton and its diseases; for example accessory ossicles are developmental variants which are often asymptomatic; when incidentally picked up on imaging, they are often inconsequential and rarely a cause for concern. However, they may cause pain or discomfort due to trauma, altered stress, and over-activity, so a correct identification can be useful to guide treatment and clinical evaluation. Fluorine-18-NaF has an important role in the study of tissues' calcification; it is possible to find unexpected atypical uptake within a calcified left ventricular wall which may be related to a dystrophic or an idiopathic cause or within the iliopsoas muscle due to myositis ossificans (figure 32). Sometimes, ^{18}F-NaF can reveal unexpected uptake in correspondence of cerebral infarct or calcified thyroid nodule as

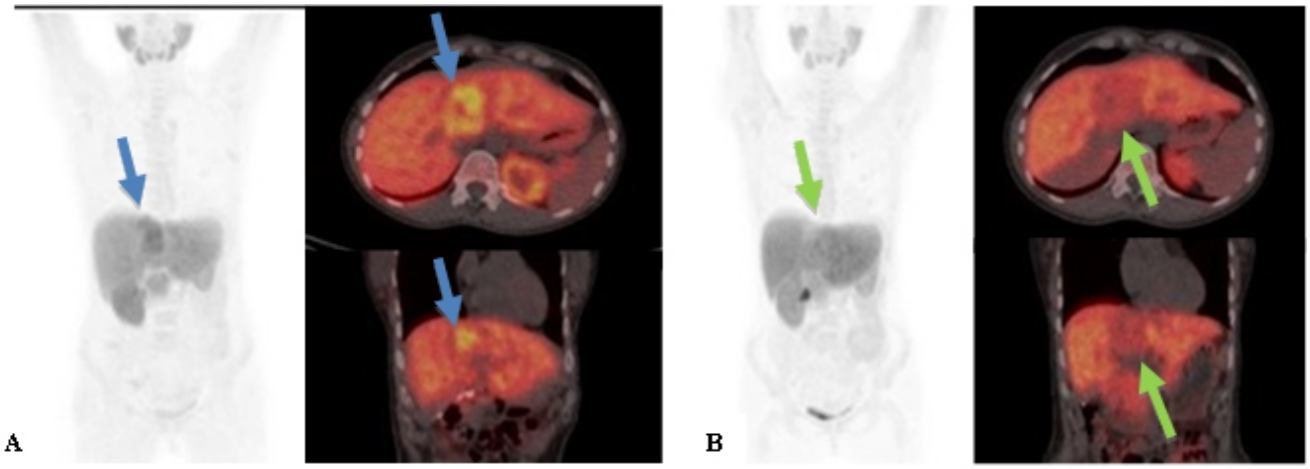

Figure 30. A 35 year old woman, evaluated with ^{18}F-FCH PET/CT for Focal Nodular Hyperplasia (FNH) of VIII-IV-I hepatic segments. A: Pre-treatment ^{18}F-FCH PET/CT: expected increased uptake in the Focal Nodular Hyperplasia (VIII-VI-I segments). Treatment with yttrium-90 (^{90}Y). B: Post-treatment ^{18}F-FCH PET/CT: expected decreased uptake area in I-IV hepatic segments (treatment result).

occasional findings (Figures 33, 34) [47].

Figure 32. Fluorine-18-NaF unexpected but typical uptake within the iliopsoas muscle due to myositis ossificans [47].

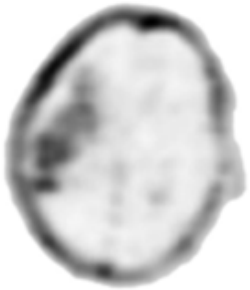

Figure 33. Unexpected atypical cerebral infarct [47].

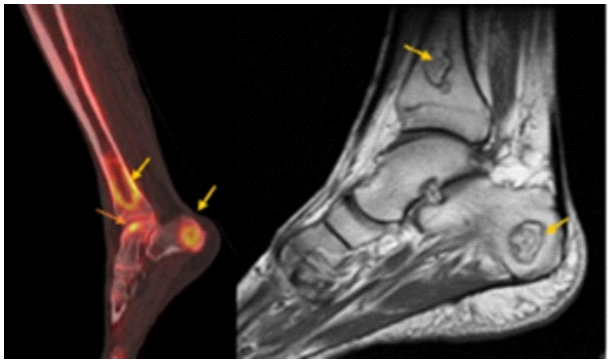

Figure 34. Fluorine-18-NaF unexpected but typical uptake in the right distal tibia and right calcaneus (yellow arrow) due to bone infarctions, plus the right talar dome (red arrow) due to the osteochondral injury [48].

In conclusion, it is important to describe unexpected occasional typical or atypical PET/CT findings whitin scientific and medical community; it can be the starting point to the enlargement of PET/CT indications for a better and wider comprehension of the function of different organs and tissues.

In order to recognize unexpected occasional finding, the nuclear medicine physician has to be aware of many aspects: physiological biodistribution, diagnostic imaging instrumentations and techniques, pathological aspects of the different neoplasmatic diseases, patient story, such as previous therapy, and its comorbidity.

An unexpected occasional finding can lead to suggest further tests or investigations in order to have a wider comprehension of patients' clinical situation.

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