Postoperative granulomas versus tumor recurrence: PET and SPET scans as strategic adjuvant tools to conventional neuroradiology

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Abstract

A mandatory differential diagnosis between postoperative granulomas and tumor recurrence is required whenever space-occupying lesions are detected at the surgical site, few months after removal of the intracranial neoplasm, because these two pathologies can often mimic each other clinically, by imaging techniques and even macroscopically. Since history or signs of inflammation may be lacking, and neurological complaints are generally nonspecific, a thorough imaging investigation is usually the only way to diagnosis. Herein we discuss the pathological basis and timing of granuloma formation along with the imaging characteristics and nuclear medicine findings necessary to confirm or exclude the diagnosis of tumor recurrence. *In conclusion*, the high sensitivity of positron emission tomography and the wide availability of single photon emission tomography can identify certain parameters (isometabolism, uptake in macrophages, etc.) to support differential diagnosis between postoperative granulomas and tumor recurrence.

Introduction

Postoperative intracranial granulomas are reported to occur anywhere, months to decades after surgical procedures, being the expression of a chronic "in situ" inflammation characterized by accumulation of modified macrophages and initiated by a variety of infectious and non-infectious agents. As for other non-neoplastic postoperative changes, their prompt identification in neuro-oncological patients is important to prevent inappropriate treatment of presumed tumor recurrence. Nevertheless, since history or signs of inflammation may be lacking, and neurological complaints are generally unspecific, an investigation by imaging modalities is commonly the only tool available to make a difficult choice between conservative medical treatment and aggressive surgical intervention.

We shall discuss the pathological basis and timing of granuloma formation along with nuclear medicine findings necessary to confirm or rule out the suspicion of tumor recurrence.

Pathological basis of postoperative space occupying lesions

Up to date, 47 cases of "intracranial postoperative granuloma", ranging from aneurysm surgery, tumor excision, ventricular drainage or Gasserian ganglion decompression, have been reported in the literature. The suspicion for inflammation at the surgical site can be raised by clinical signs or biomarkers [1]. Whilst clinical signs depend on the localization of the lesion, and are very unspecific with regard to its nature, inflammation markers represent an important first step to consider in the diagnostic flow-chart. Specifically, serum procalcitonin has a sensitivity of 76% and a specificity of 70%, while C-reactive-protein (CRP) appears to be more accurate, since it rises progressively up to 50,000-fold in acute inflammation. Moreover CRP levels in chronic inflammations are mainly determined by the rate of production generally ranging between 10-200mg/L being much more higher in bacterial than in viral infection (note that normal values are: <10mg/L; values in viral infections are: <40mg/L; values in bacterial infections are: >40 <200mg/L; values in burns >200mg/L) [2].

A variety of sutures, dural substitutes and local hemostatics are routinely used in neurosurgery. Every material left in the surgical site, including absorbable material, such as gel foam, microfibrillar collagen, oxidized cellulose, fluid hemostatics, or non-absorbable material, such as bone wax, cotton pledgets, rayon, and polytetrafluoroethylene has been shown to carry a certain risk of granuloma formation [1, 3, 4].

Most of these materials are expected to dissolve promptly, while others are meant to last during patients' life. Accordingly, the risks of side effects, such as local inflammation and allergic response depending on the individual hypersensitivity and antigenicity for the product used, may be variable for every agent and for every patient.

As a rule, when such materials are retained at the surgical site, near the bone or brain parenchyma, documentation such as surgical reports, duly indicating the chemical or physical characteristics of the products used, specific patients' identification cards reporting the date of implantation, the type of intervention and manufacturer's data are important. This information is an indispensable reference for the interpretation of postoperative brain changes.

Conventional Neuroradiology

Postoperative granulomas are reported to occur several months or even years after brain surgery, eventually mimicking tumor recurrence [3, 4]. Some imaging guidelines for the analysis of postoperative changes suggest that the presence of a visible ring of density on a pre-contrast computerized tomography (CT) scan, six months after brain surgery is more likely due to malignancy than to a benign condition, such as aseptic postoperative inflammation or other non-tumoral imaging changes [5].

Feldman et al. (1999) proposed magnetic resonance imaging (MRI) findings of low intensity on T1-weighted images and heterogeneous high intensity on T2-weighted images, as being the rule for intracranial postoperative granulomas [6]. The advancement of knowledge in the field of postoperative imaging changes, with special reference to parenchymal reaction to retained foreign bodies, showed that diffusion weighted (DW) images could be crucial in distinguishing between granulomas and exudates; suggesting that the glial inflammation and the vascular/cytotoxic oedema occurring in postoperative granulomas might be primarily responsible for hyperintensity on the T2-weighted and on FLAIR MRI images [4]. Recently, further information accumulated from the analysis of tissue metabolites such as N-acetylaspartate, choline, creatine, lactate glycine and myo-inositol, or on the ratio among them (in particular choline/N-acetylaspartate and cholin/creatine). This information is even more useful in characterization, grading and recurrence of tumors but also in detecting and interpreting a wide range of non-tumoral pathologies [7]. Along with information retrieved by relative cerebral blood volume as well as by apparent diffusion coefficient, the above imaging patterns have transformed the latest MRI techniques, namely spectroscopy, perfusion and diffusion into the state of the art of pre- and postoperative neuroradiological investigation.

PET, SPET and future applications of Nuclear Medicine

To date, positron emission tomography (PET) is the most powerful method for in vivo imaging of brain metabolism, and is also well accepted in grading brain tumors since, by assessing the maximal standardized uptake value and the tumor-to-normal tissue ratio, almost every metabolic feature of brain lesions, including postoperative granulomas, can be detected (see Fig. 1 for an exemplificative case). Fluorine-18-fluorodeoxyglucose (^{18}F-FDG) represents the first PET tracer effectively used for the evaluation of brain tumors as well as non-tumoral brain lesions [8]. The main reason for the success of ^{18}F-FDG PET is its high sensitivity for brain tumor and particularly its higher specificity than CT and MRI [9, 10]. However, its 10%-15% of false-positive results, and the understanding that amino acid transport and protein metabolism are significantly upregulated in brain tumors in comparison with normal brain tissue and inflammatory sites, led in recent years to an increasing number of tracers (like labeled methionine, tyrosine, thymidine, choline, fluoromisonidazole, and so forth) to being tested. As a result, radiolabeled amino acid analogs, such as O-(2-^{18}F-fluoroethyl)-L-tyrosine (^{18}F-FET), were suggested to be even more specific and sensitive in tumor imaging than ^{18}F-FDG [11, 12]. Then, ^{11}C-methionine (^{11}C-MET) appeared to be the radiotracer of choice in the evaluation of recurrence of primary brain tumors, because of its high sensitivity for the detection and delineation of possible recurrent primary tumors, as well as for metastases. The ^{11}C-MET used with PET is a more affective technique to diagnose a neoplastic formation than ^{18}F-FDG and with less interobservers variability [13]. Glial infiltration in the brain can be confirmed when high ^{11}C-MET uptake is observed because of its high tumor to brain activity ratio [11]. Moreover brain lesions showing hypo-metabolism, like: low grade gliomas, meningiomas, etc. or isometabolism, like granulomas were well detected and differentiated with high sensitivity by using ^{11}C-MET PET [14]. Whilst, in terms of definition of boundaries ^{11}C-MET is also considered better than other tracers or conventional neuroimaging [15], on the other hand ^{11}C-MET uptake could be more affected than ^{18}F-FDG by cerebral blood volume (CBV) within the tumor [13].

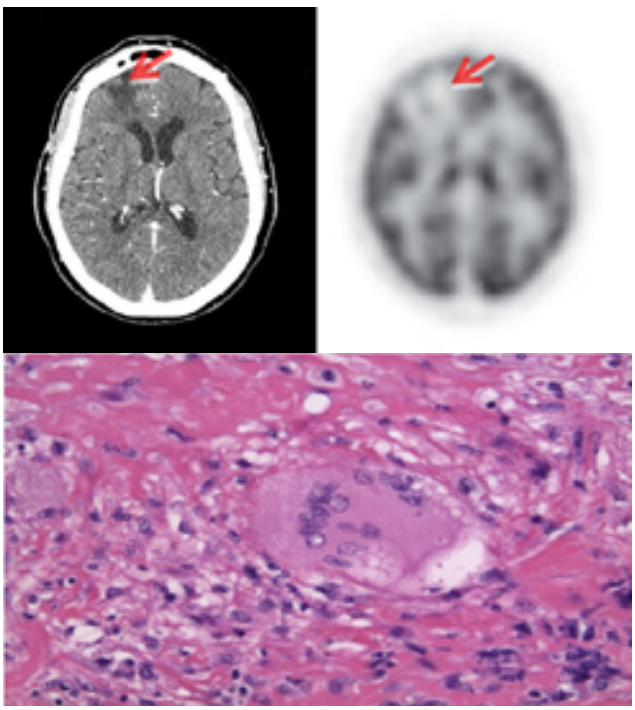

Figure 1. CT (top right) and ^{18}F-FDG PET (top left) of a patient with postoperative radiological changes: appearance of a low-enhanced right frontal lesion surrounded by a remarkable parenchimal edema corresponding to a iso-hypometabolic area on PET images (see arrows); despite the ^{18}F-FDG PET data concerns about glioma recurrence were raised. Postoperative Histological Sample (Bottom): the hematoxylin-eosin staining (magnification 100x) shows giant multinucleate cells, typical elements of postoperative granulomas, along with acellular zones; the suspect of tumor recurrence is definitely ruled out.

These achievements of nuclear medicine even in the diagnosis of benign tumors have been confirmed not only by the usual histological examination but also with more accurate and sophisticated pathological techniques. Researchers reported that ^{18}F-FDG uptake significantly correlates with neoplastic proliferation indexes (such as MIB-1 labelling index) and with the mitotic count in meningiomas, thus reflecting their proliferative activity [16]. Similar results were found by other researchers with ^{11}C-MET showing that its uptake in meningiomas significantly correlated with the Ki-67 proliferative index, thus allowing for the detection and prediction of benign tumors recurrence [17]. To specifically regard with postoperative imaging changes, other

Table 1. *Summary of the most relevant studies discussed in the present paper*

	Main Findings	Reference
PET SCAN		
^{18}F-FDG	uptake proportional to the amount of viable cells	Iuchi et al 1999
	correlation with neoplastic proliferation indexes (MIB-1)	Lee et al 2009
	useful in differentiating tumor recurrence from malignant transformation in low-grade tumors	Seiz et al 2008
^{18}F-FET	more specific and sensitive than ^{18}F-FDG in imaging of aggressive tumors	Wester et al 1999
^{11}C-MET	better than other tracers or conventional neuroimaging in definition of tumor boundaries in aggressive tumors	Tovi et al 1990
	useful in differentiating tumoral from non-tumoral lesions	Chung et al 2002
	useful in detection and prediction of benign tumors recurrence	Herholz et al 1998 Kubota et al 1995
	more affected than ^{18}F-FDG by cerebral blood volume	Tripathi et al 2012
SPET SCAN		
^{201}Tl	useful in differentiating tumor recurrence from radiation necrosis in aggressive tumors	Matsunaga et al 2012
	useful in predicting early progression in low-grade tumors	Park et al 2012
^{99}Tc-TF	correlation with histological grade and proliferation index in low-grade tumors	Fotoupoulos et al 2008
	correlation with tumor aggressiveness in low-grade tumors	Alexiou et al. 2008
citric acid labeled radionuclides	easy preparation, low cost and early accumulation in intracranial postoperative inflammatory lesions	Hoep et al. 2006

studies confirmed that the uptake of ^{11}C-MET, like that of ^{18}F-FDG PET is proportional to the amount of viable cells and is low in macrophages and other non-tumoral cellular components, making ^{11}C-MET PET extremely helpful in the diagnosis of various non-tumoral lesions [15, 18, 19]. Thus, the selection of a suitable tracer depends on the type of tumor and aim of the test, since each tracer has unique uptake properties, and often the combination of both ^{18}F-FDG and ^{11}C-MET provides complementary information (see Table I for a general summary of the main findings from the discussed studies).

Despite the fast-growing use of PET, single-photon emission tomography (SPET) studies are often adequate in the postoperative follow up of brain tumors, providing results that parallel those obtained with PET [20, 21]. Not requiring an onsite cyclotron (essential prerequisite for ^{11}C-MET PET), SPET has wider availability and lower cost, nevertheless its principal limitation exploiting brain tumor-seeking radiopharmaceuticals is the lack of precise anatomic details. In the past, this drawback was bypassed with software-based fusion of independently performed SPET and CT or MRI, but this time-consuming process is no more necessary due to the recent development of dual-modality integrated imaging systems, which allows for the acquisition and co-registration of SPET and CT images in the same scanning session [13].

To date, cerebral SPET studies are helpful in providing precise localization of neoplastic and inflammatory lesions and in excluding disease in sites of physiologic tracer uptake. Thallium-201 (^{201}Tl), one of the first tracers introduced in clinical practice, is useful for interpreting postoperative imaging changes, in particular by differentiating tumor recurrence from radiation necrosis in patients operated for malignant brain tumors [22]. Other researchers showed its usefulness in predicting early progression even in low-grade astrocytomas [23]. Furthermore, the uptake of technetium-99-tetrofosmin (^{99}Tc-TF), a SPET tracer specific for brain tumors, proved to correlate with aggressiveness and proliferation index in malignancy and in meningiomas [24-26]. Finally, due to their ideal physical characteristics, easy preparation, low cost, early accumulation and the preference for the renal route of excretion, citric acid labeled radionuclides (i.e.: gallium-68-citrate t/2: 68min; yttrium-90-citrate t/2: 2.67days; gallium 67-citrate t/2: 3.26days) showed effectiveness for the visualization of intracranial inflammatory lesions even postoperatively [27]. Thus, despite its abovementioned limits, also SPET scan confirms to be a valid aid in providing differential diagnosis nuances for the management of postoperative granulomas (see Table 1 for a general summary of the main findings from the discussed studies).

In conclusion, nuclear medicine may be diagnostic in ruling out postsurgery tumor recurrence or granulomas by yielding information on hemocirculatory and metabolic aspects of these pathologies. The combination of multimodal neuroimaging techniques such as MRI, PET and SPET is even more effective to diagnose granulomas by changes like parenchymal edema and integrity of fiber structures.

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