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PET/CT for Inflammatory Diseases

Basic Sciences, Typical Cases, and Review

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Foreword

In 2013, when I was the president of the Japanese Society of Nuclear Medicine, an inter-society agreement (MOU) was signed between the Japanese Society of Nuclear Medicine and the Chinese Society of Nuclear Medicine organized by the president, Prof. Gang Huang. After that, according to this MOU, Prof. Jun Hatazawa, my successor president, and Prof. Yaming Li, successor to Prof. Huang, have been carrying out exchange project that is unparalleled in the history of Japanese and Chinese nuclear medicine. The exchange has been becoming active year by year these 5 years.

The project accomplished many presentations of both sides at the conference. In addition, we visited each other's nuclear medicine facilities for a short time to deepen our relationship. From an academic point of view, collaborators were collecting and examining cases based on a common understanding of the theme of FDG PET inflammatory diseases. As an excellent result of symposium for this trial in 2017 Asia Oceania Congress of Nuclear Medicine and Biology (AOCNMB 2017), the publication of this textbook was planned by Dr. Hiroshi Toyama and Dr. Yaming Li with support of Springer Co. This textbook is well organized from basic science (Chap. 1) to clinical cases based on etiologies of infectious/inflammatory diseases (Chaps. 2–8). This book is written by veterans and young nuclear medicine physicians representing both countries, and I believe this textbook is a good reference for nuclear medicine physicians and researchers. This book is a testament to the fact that Japan-China nuclear medicine exchanges have been carried out substantially.

I would like to pay tribute for the efforts of Dr. Hiroshi Toyama and Dr. Yaming Li who have deepened nuclear medicine exchanges between China and Japan.

Tomio Inoue
Shonan Kamakura General Hospital, Iryohojin
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Preface

On behalf of the organizing committee of Japan-China Nuclear Medicine Exchange Program and Japanese Society of Nuclear Medicine and as one of the editors, I am pleased to publish the textbook entitled *PET/CT for Inflammatory Disease: Basic Sciences, Typical Case Series, and Review* from Springer Co.

The contents of this book consist of eight chapters. In Chap. 1, overview of the basic science of PET imaging for inflammatory diseases is written. From Chaps. 2 to 8, typical case reports and review using PET imaging are written in each category of inflammatory disease.

Regarding the opportunity for publication of this book, for the first step, we have discussed the international joint research regarding ^{18}F-FDG PET/CT imaging for diagnosis of inflammatory disease at the task force meeting of Japan-China Nuclear Medicine Exchange Program on November 4, 2016, at the 56th Annual Meeting of Japanese Society of Nuclear Medicine in Nagoya. For the second step, we, Japanese and Chinese, discussed about PET imaging for inflammatory diseases at the eighth Sino-Japan Nuclear Medicine Exchange Seminar in 2017 Asian Nuclear Medicine Academic Forum on May 13, chaired by the Asian School of Nuclear Medicine (ASNM) Dean, Prof. Guan Huang. For the third step, the Japan-China Nuclear Medicine joint symposium entitled "FDG PET for Inflammatory Disease" was carried out at the 57th Annual Scientific Meeting of the Japanese Society of Nuclear Medicine and the 12th Asia Oceania Congress of Nuclear Medicine and Biology in Yokohama, Japan, October 7, 2017, headed by President Tomio Inoue, MD, PhD, professor and chairman, Yokohama City University Graduate School of Medicine. Several Japanese and Chinese physicians presented and discussed about various inflammatory diseases using PET imaging. Based on these consecutive steps, we have decided to publish the textbook regarding PET for inflammatory disease as a commemoration of the fifth anniversary of Japan-China Nuclear Medicine Exchange Program. I am really proud for publishing this book based on many people' s efforts and supports from both Japan and China sides. Finally, I appreciate Dr. Mototora Kai, secretary general of the ASNM, people of Sino-Japan Nuclear Medicine Exchange Association, Japan-China Nuclear Medicine Exchange Committee, and Springer Co.

Toyoake, Aichi, Japan — Hiroshi Toyama

Preface

In China, both the numbers of PET/CT installation and the numbers of clinical examination are increasing in recent years. According to the national survey made by the CSNM in 2017, more than 90% of cases examined by PET/CT in China were due to diagnosing, efficacy evaluation of treatment, or prognosis evaluation of tumors.

PET/CT imaging is an important representative of molecular imaging. With one whole body imaging, lesions in tissues and organs examination can be detected with high sensitivity. However, the potential and feasibility of its application in non-tumor diseases need to be further explored and expanded.

The incidence of inflammatory and infectious diseases is high, but the clinical manifestations are often non-specific. Thus, its clinical diagnosis is very challenging. PET/CT imaging, as a highly sensitive whole body imaging, has great prospects for its application in the diagnosis. However, the application of PET/CT imaging in these diseases is rarely included in the relevant guidelines, and high-level evidence-based medical evidence is still needed in this regard. Based on the status quo, China and Japan have jointly carried out a multicenter study on the application value of PET/CT imaging in unexplained fever. To investigate the diagnostic value of ^{18}F-FDG-PET/CT for FUO and IUO and the imaging characteristics of PET/CT in the diseases of different etiology, the results of ^{18}F-FDG-PET/CT examinations of 376 FUO/IUO patients in 12 hospitals in China were analyzed. The clinicians were also surveyed to evaluate the significance of PET/CT in the diagnosis of FUO/IUO. The results showed that among 376 patients, infectious diseases accounted for 33.0%, rheumatism for 32.4%, malignant tumors for 19.1%, miscellaneous factors for 6.6%, and unexplained for 8.8%. According to the clinical questionnaire, 77.4% of patients provided additional diagnostic information, and 89.6% of patients benefited from.

^{18}F-FDG-PET/CT is a valuable tool for clinical diagnosis of FUO/IUO. Its application in inflammatory and infectious diseases requires in-depth research and exploration. This book describes the application, basic knowledge, and typical lesions of PET/CT imaging in inflammatory diseases. It can provide help for the accurate and effective application of PET/CT imaging in inflammatory diseases, provide objective basis for the diagnosis and treatment of those patients, and further promote the wider application of related diagnostic techniques in China.

I sincerely thank Professor Hatazawa and Professor Toyama of Japan for their efforts on organization and guidance on the edition of this book. I sincerely thank all the authors from Japan and China who participate in the writing of this book.

Shenyang, Liaoning, China — Yaming Li

Preface

On behalf of all the contributors to publish this textbook, I would like to express sincere gratitude to Prof. Tomio Inoue and Prof. Huang Gang who initiated the China-Japan Exchange Collaboration Program in nuclear medicine since 2011. The Program was expanding every year. Physicians, technologists, researchers, and nurses bilaterally joined more and more in any occasions of the workshop and on-site education/training in the hospitals. Under the leadership by Prof. Yaming Li, Prof. Hiroshi Toyama, and Dr. Kazuo Kubota, we came to this book, a harvest of our friendship and academic achievement.

In the 14th International Conference on Radiopharmaceutical Therapy (ICRT) held in Nanjing on August 21–24, 2019, I learned the origin of thyroid therapy conducted by Dr. Saul Hertz, Thyroid Clinic of Massachusetts General Hospital, in 1942 by means of Iodine-131 to treat hyperthyroidism and later thyroid cancer. His daughter presented the old history of radioactive iodine use for therapy by the founders of the radiopharmaceutical therapy.

This book focuses on diagnosis of "inflammation," an alternative value of FDG PET/CT. FDG applications to benign and malignant diseases are quite similar to the application of Iodine-131. It will significantly contribute to understanding of FDG PET/CT in the clinical practices and will further facilitate more cancer-specific PET tracers than ever.

Based on this achievement by clinicians and researchers in China and Japan, we together go forward to improve our specialty and to foster nuclear medicine professionals for the next generation.

Suita, Osaka, Japan — Jun Hatazawa

Preface

PET Imaging and Inflammation

Positron emission tomography–computed tomography is an advanced medical device, which is a successful clinical application of the molecular imaging technique and a good tool for the transition to clinical application from molecular biology research. Moreover, PET/CT is the true carrier of clinical medicine from experience to precision medicine. The application of ^{18}F-FDG PET (PET/CT) in tumor diagnosis, staging, and efficacy prediction and evaluation has become a clinical routine. The application of PET (PET/CT) in brain science and neuropsychiatric diseases has become another highland for the development of molecular imaging technology in the future. Many domestic and foreign scholars use PET (PET/CT) to visualize a variety of physiological, biochemical, and pathophysiological processes in humans. It is like a guiding light in the ocean of transformation of medicine, leading the course of future development of medicine.

The inflammatory reaction is a complex pathophysiological reaction of human tissues and organs to various physical, chemical, immunological, or microbial damages and is the most important adaptive process for the body defense. The inflammatory reaction could be caused by various external and internal inflammatory factors, including biological factors, physicochemical factors, and immune responses. The physiological and pathological processes of the inflammatory response mainly include alteration, exudation, and proliferation. With the development of modern molecular biology techniques, the physiological and pathological processes of inflammatory reactions have evolved from descriptive structural change of the tissues under optical microscope to the interpretation of the change and regulation of different cells and different biomolecules during the process of inflammatory reaction. Molecular imaging technology accurately and objectively visualizes the changes of different biomarkers in the inflammatory response process, helping clinical accurate diagnosis and guiding precise treatment.

^{18}F-deoxyglucose (2-deoxy-2-^{18}F-fluoro-D-glucose, ^{18}F-FDG) is the most widely used PET imaging agent. ^{18}F-FDG is a glucose analog, which will be phosphorylated to ^{18}F-FDG-6-PO4 by hexokinase and remains trapped in the cells. ^{18}F-FDG is mainly used in the clinical diagnosis, staging, and efficacy evaluation of tumor. Inflammatory cells such as macrophages will undergo "breath excitement" when functioning, and macrophages require high uptake of glucose, resulting in increased uptake of ^{18}F-FDG in the inflammatory lesions; therefore the PET imaging result will be positive [1, 2]. ^{18}F-FDG PET/CT has become a clinical routine in the search for infections in unexplained fever. Macrophages uptake glucose highly, and the molecular signaling and mechanism that induce changes in the inflammatory response process have become a hotspot in the study of inflammation and metabolism.

^{111}In-8 hydroxyquinoline (^{111}In-oxine) and 99mTc-6-methyl propylenediamine (99mTc-HMPAO)-labeled leukocytes have been widely used clinically in SPECT imaging and have obtained positive value. However, PET imaging of labeled leukocytes is still in the clinical research stage, including molecular probes labeled with different nuclides such as ^{18}F, ^{64}Cu, and 89Zr [3]. ^{68}Ga-pentixafor is used for synovial angiogenesis imaging of rheumatoid arthritis [4]. The ligand of CXCR4 and ^{68}Ga-pentixafor utilizing the specificity of CXCR4 as a

radiotracer for CXCR4 expression could be used for chronic inflammation imaging of bone [5]; ^{18}F-PEG-folate for rheumatoid arthritis active imaging; and ^{124} I-FIAU for bacterial infection imaging [6].

Inflammation can also directly or indirectly lead to a variety of diseases, including atherosclerosis, autoimmune diseases, and Alzheimer's disease. ^{18}F-NaF PET-CT could be used to evaluate the microcalcifications and its levels in atherosclerotic plaques, and it is the first non-invasive imaging method to identify and locate ruptured plagues and high-risk coronary atherosclerotic plaques [7]. Other imaging agents capable of visualizing atherosclerotic plaques and predicting ruptured plaques include targeted macrophage inflammatory imaging (somatostatin receptor analog SSTR, ^{11}C-choline, ^{68}Ga-pentixafor, ^{11}C-PK11195) and inflammation and neovascular imaging agent integrin αVβ3 [8, 9]. TSPO PET can be used to assess neuroinflammation and play an important role in the assessment of disease progression, prognosis, and efficacy of multiple sclerosis [10, 11].

Inflammation molecular imaging technique could provide real-time information that plays an important role in disease diagnosis, prognosis, treatment, reaction monitoring, and understanding the nature of diseases. Targeted imaging agents with different biomarkers used in PET/CT or PET/MR will also contribute to the visualization and quantitative diagnosis of inflammatory diseases. As people have a better understanding of the inflammatory response of various disease types, researchers will look for more sensitive and more specific biomarkers and develop them into new inflammatory imaging probes.

As an important monograph of PET/CT in the exploration of inflammation and mechanism, this book will provide a valuable reference for clinical medicine and basic inflammation research. I sincerely appreciate all the experts who have dedicated their time and effort to this book: your enriched experience and wisdom will enhance the value of this book.

Shanghai, China Guang Huang

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Contents

Basic Science of PET Imaging for Inflammatory Diseases

1

Kazuo Kubota, Mikako Ogawa, Bin Ji, Tadashi Watabe, Ming-Rong Zhang, Hiromi Suzuki, Makoto Sawada, Kodai Nishi, and Takashi Kudo

1.1 Mechanisms of FDG Accumulation in Inflammation

Kazuo Kubota

Abstract FDG-PET/CT has recently emerged as a useful tool for the evaluation of inflammatory diseases too, in addition to that of malignant diseases. The imaging is based on active glucose utilization by inflammatory tissue. Autoradiography studies have demonstrated high FDG uptake in macrophages, granulocytes, fibroblasts, and granulation tissue. Especially, activated macrophages are responsible for the elevated FDG uptake in some types of inflammation. According to one study, after activation by lipopolysaccharide of cultured macrophages, the [^{14}C]2DG uptake by the cells doubled, reaching the level seen in glioblastoma cells. In activated macrophages, increase in the expression of total GLUT1 and redistributions from the intracellular compartments toward the cell surface have been reported. In one rheumatoid arthritis model, following stimulation by hypoxia or TNF-α, the highest elevation of the [^{3}H]FDG uptake was observed in the fibroblasts, followed by that in macrophages and neutrophils. As the fundamental mechanism of elevated glucose uptake in both cancer cells and inflammatory cells, activation of glucose metabolism as an adaptive response to a hypoxic environment has been reported, with transcription factor HIF-1α playing a key role. Inflammatory cells and cancer cells seem to share the same molecular mechanism of elevated glucose metabolism, lending support to the notion of usefulness of FDGPET/CT for the evaluation of inflammatory diseases, besides cancer.

Keywords: Macrophage, Neutrophil, Fibroblast, Granulation tissue, GLUT, HIF-1α, FDG

1.1.1 Introduction

Fluorine-18-labeled 2-deoxy-2-fluoro-glucose (FDG) is used as a radiopharmaceutical in PET for evaluating glucose metabolism, and accumulates in malignant tissues because of the enhanced glucose utilization by neoplastic cells. Because of the increased metabolic demand for glucose,

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elevated activity of hexokinase and elevated expression of glucose transporter have been shown in tumor tissues [1]. Various applications of FDG-PET have been extensively studied in the field of clinical oncology, and the imaging modality, now used worldwide, is recognized as a powerful diagnostic modality for cancer [2, 3]. In 1989, elevated FDG uptake was reported in two patients with abdominal abscesses [4]. This was followed by reports of FDG uptake in brain abscess [5], tuberculosis, aspergillosis, sarcoidosis, and so on. In addition, early postoperative scarring and early inflammatory reactions after radiotherapy were also reported to show increased FDG uptake. Thus, elevation in glucose metabolism is not only specific for cancer but also seen in inflammation. Because FDG uptake is seen in benign inflammatory diseases as well, the accuracy of FDG-PET for the diagnosis of cancer is not 100% [6].

1.1.2 FDG Uptake by Inflammatory Tissues and Cells

Although the metabolic fate of FDG is well known, its cellular distribution within tumors or sites of inflammation has not yet been described. To clarify the mechanisms of FDG uptake by inflammatory and tumor tissues, we performed autoradiographic studies. To demonstrate the cellular localization of FDG and [^{3}H]2DG uptake by tumors in vivo, C3H/He mice with subcutaneously transplanted FM3A tumors were studied 1 h after intravenous injection of FDG or [^{3}H]2DG. Newly formed granulation tissue around tumors and macrophages, which had massively infiltrated the marginal areas surrounding the necrotic areas of the tumor, showed a higher FDG uptake than the viable tumor cells. A maximum of 24% of the glucose utilization was derived from the non-neoplastic tissues in these tumors (Fig. 1.1). The strong accumulation of FDG in these tumors was thought to represent both the high metabolic activity of the viable tumor cells and that of the tumor-associated inflammatory cells, especially activated macrophages. These results indicate that not only glucose uptake by the tumor cells but also that by non-neoplastic cellular elements which appear in association with the growth or necrosis of tumor cells should be considered for a precise analysis of FDG uptake in tumors, especially after radiotherapy (Fig. 1.2) [7, 8].

FDG uptake by inflammatory tissues was investigated by Yamada et al. [9]. A rat model of chemically induced inflammation using turpentine oil was used. A time-course study of the FDG tissue distribution showed that the uptake of FDG

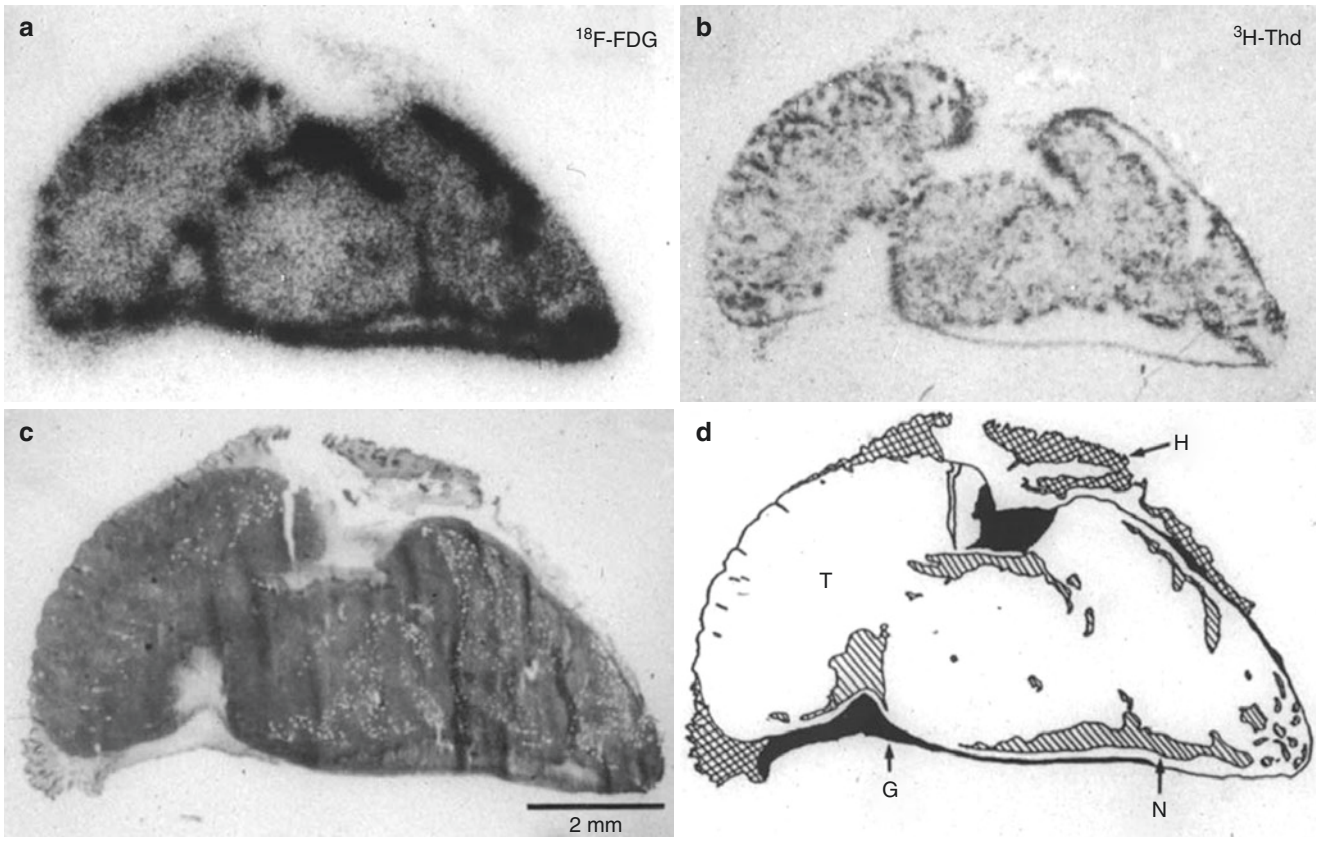

Fig. 1.1 A combination of double-tracer macro-autoradiograms and microscopy. Images of 18F-FDG distribution (**a**) and 3HThd (**b**), a photomicrograph of the tissue specimen (**c**) and an illustration of the micrograph (**d**). *T* tumor calls, *G* granulation tissue, *N* necrosis, *H* host normal tissue. Scale bar: 2 mm. Newly formed granulation tissue around the tumor and macrophages infiltrating the periphery of the necrotic areas of the tumor showed higher uptakes of FDG than the viable tumor cells. (From Ref. [7])

in inflammatory tissue increased gradually until 60 min, followed by a steady decrease thereafter. A longitudinal study showed that the uptake increased progressively after the start of inflammation, peaking at 4 days after the inoculation, and then gradually decreased (Fig. 1.3). These findings suggested that FDG uptake may reach a maximum during the subacute phase of inflammation, and then slightly decreases during the chronic phase of inflammation. An autoradiography study showed a high FDG uptake in the abscess wall, consisting of an inflammatory cell layer and granulation tissue. At the cellular level, the highest radioactivity was found in the marginal zone that contained young fibroblasts, endothelial cells of vessels, and phagocytes consisting of neutrophils and macrophages, followed by that in the neutrophil layer and the granulation tissue layer (Fig. 1.4). FDG uptake by inflammatory tissue seems to represent the activity of immune cells and fibroblasts mobilized to the lesion.

Mochizuki et al. [10] compared the FDG uptake by experimental hepatoma and by tissue with experimental infection with *Staphylococcus aureus*. The expressions of GLUT1 and GLUT3 were also studied in both the tumor and infected tissue by immunostaining. Uptake by the tumor tissue was significantly higher than that by the infected tissue. Both the tumor and infected tissue showed strong expression of GLUT1 and GLUT 3, although the expression level of GLUT1 was significantly higher in the tumor than in the infected tissue. GLUT1 may be responsible for FDG uptake in both tumor tissue and infected tissue.

Zhao et al. [11] compared the two models of inflammation: BCG-induced granuloma simulating sarcoidosis and

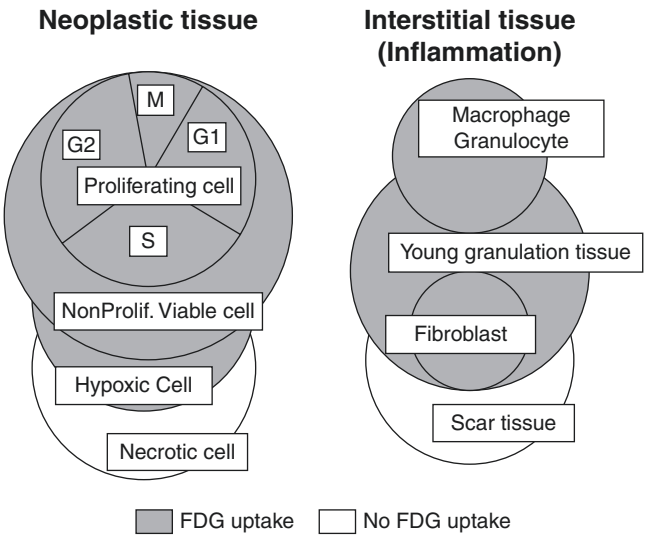

Fig. 1.2 A model of FDG accumulation in various cellular elements in a tumor. (Modified from Ref. [8])

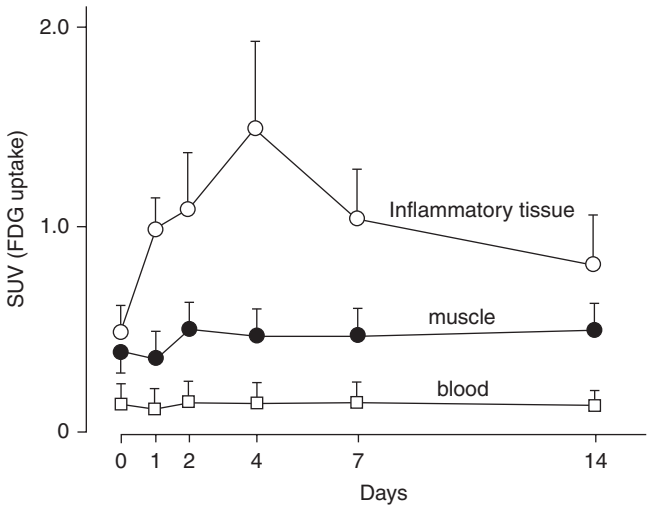

Fig. 1.3 FDG uptake changes along with the age of inflammation. FDG uptake by inflammatory tissue, muscle, and blood are plotted against the days after inoculation of turpentine oil. The highest uptake by inflammatory tissue was observed on day 4, which represented the subacute phase histologically ($n = 5$, each point). (From Ref. [9])

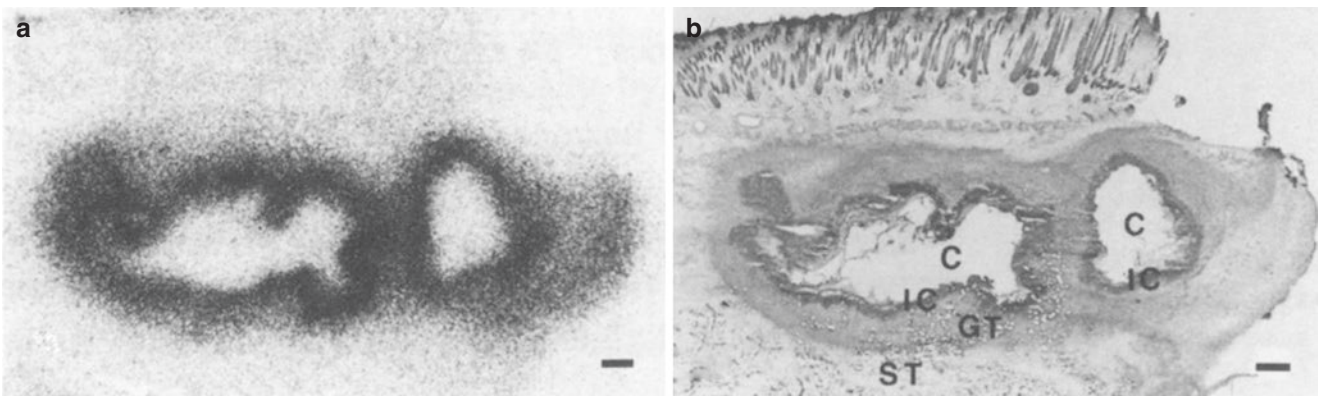

Fig. 1.4 Macro-autoradiogram (**a**) and the corresponding section (**b**) of inflammatory tissue 4 days after inoculation of turpentine oil. The center (C), surrounded by inflammatory cells (IC), thick granulation tissue (GT), and edematous subcutaneous tissue (ST). Scale bar 0.4 mm. (From Ref. [9])