The Role of ^{18}F-Fluorodeoxyglucose Positron-Emission Tomography/Computed Tomography in the Diagnosis of Postoperative Hardware-Related Spinal Infections

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ABSTRACT: **Background:** Implant-related spinal infections are a surgical complication associated with high morbidity. Due to infection, hardware removal may be necessary, which could lead to pseudarthrosis and the loss of stability and alignment.

Objectives: To evaluate the accuracy and diagnostic value of ^{18}F-fluorodeoxyglucose positron-emission tomography/computed tomography (^{18}F-FDG PET/CT) in the workup of patients with suspected implant-related infections of the spine and to assess the clinical impact of PET/CT results on the management of these infections.

Methods: The study included nine consecutive patients with a history of spinal surgery who underwent PET/CT for evaluation of suspected spinal implant related infection. All imaging studies were performed between January 2011 and December 2013. All ^{18}F-FDG PET/CT scans were performed on an 8 slice PET/CT following an ^{18}F-FDG injection. Images were scored both visually and semi-quantitatively by a radiology expert. Results were compared to additional imaging studies when available, which were correlated to clinical and bacteriological findings allowing calculation of sensitivity, specificity and accuracy.

Results: Among the patients, five experienced hardware-related spinal infection. ^{18}F-FDG PET/CT sensitivity was 80%, specificity 100%, and accuracy 88.9%. One scan produced a false negative; however, a second PET/CT scan revealed an infection.

Conclusions: PET/CT was found to be valuable for the diagnosis of postoperative hardware-related spinal infection, especially when other imaging modalities were uninformative or inconclusive. As such, PET/CT could be useful for management of infection treatment.

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KEY WORDS: ^{18}F-fluorodeoxyglucose positron-emission tomography/computed tomography (^{18}F-FDG PET/CT), positron-emission tomography/computed tomography (PET/CT), skeletal imaging, spinal fusion hardware infection, surgical site infection

Postoperative spinal infections are a surgical complication correlated with high morbidity and increased costs [1,2]. These infections have a prevalence of 0.5–18.8% depending on co-morbidities, surgical technique, hardware in use, and type and complexity of the procedure [1-4].

The presentation of postoperative spinal infection can be indolent and not specific. While superficial infection involving the skin and subcutaneous tissue with obvious drainage can be easily detected, infections under the fascia involving the intervertebral discs, the vertebras, and epidural space are harder to diagnose [1]. Fever can be absent in up to half of the cases, and inflammatory markers are neither sensitive nor specific [1,2,5,6]. Common symptoms are back pain and nonspecific constitutional complaints. A physical examination may reveal erythema, local tenderness, and drainage [1,2,7,8]. Due to the nature of some of the postoperative infections, diagnosis may be delayed and infection may spread to involve the bone, paravertebral tissue, and epidural space [2,5]. This result can lead to formation of biofilm on the surface of spinal implants, preventing infiltration of antibiotics, and thus leading to persistent microbial infection. A persistent infection dictates a revision surgery for the purpose of irrigation, debridement, and removal of hardware that may result in pseudarthrosis and the loss of stability and overall alignment [2].

Several imaging techniques may improve the diagnosis of postoperative spinal infections. While X-ray images and computerized tomography (CT) scans are not highly sensitive for diagnosing early infections [2], magnetic resonance imaging (MRI) is currently the gold standard. However, although it has high sensitivity for detection of infections in the naïve spine, after surgery involving hardware, MRI is affected by postoperative changes and metallic artifacts [5,9,10].

Positron-emission tomography (PET) combined with CT is becoming more prevalent in clinical settings to detect musculoskeletal infections due to its ability to combine metabolic and anatomical imaging. While the ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET identifies increased metabolic activity as a result of the intake of glucose in inflammatory cells, the CT allows for spatial

localization of the infection. As this imaging modality is unaffected by the metallic hardware, it shows promising results in the diagnosis of such infections [1,2,6-8,10-12].

The purpose of this study was to retrospectively evaluate the accuracy and diagnostic value of ^{18}F-FDG PET/CT in the workup of patients with hardware-related infections of the spine and to assess the clinical impact of PET/CT results in the management of these infections.

PATIENTS AND METHODS

The study was approved by the institutional ethics committee at Rabin Medical Center in agreement with the Helsinki Declaration. The study comprised nine consecutive patients over the age of 18 years who were suspected of having implant-related infection of the spine and who underwent PET/CT at our medical center between 1 January 2011 and 31 December .2013 We gathered data including patient demographics and co-morbidities, type and cause for index spine surgery, type of fixation, and the reason for suspicion of infection. Inflammatory marker values at presentation included white blood cell count (WBC), C-reactive protein (CRP), and erythrocytes sedimentation rate (ESR). In addition, we also collected imaging results, surgical microbiological findings, and other required treatments.

IMAGE ACQUISITION

All ^{18}F-FDG PET scans were performed on an 8 slice PET/CT (Discovery ST, General Electric Healthcare, Milwaukee, WI, USA). Patients fasted for 4 hours prior to the ^{18}F-FDG administration, and image acquisition began 60–90 minutes after a 296–555 MBq dose 18F -FDG injection. CT images were acquired at 120 kV, 80–280 mA, pitch 0.875, and slice thickness of 2.5 mm. The CT images were reconstructed at a 1.25 mm slice thickness in bone algorithms for review. PET acquisition started immediately after in 2-D mode, 120–150 seconds/bed position, 3–4 bed positions, depending on patient size.

IMAGE EVALUATION

Projection data was reconstructed online with manufacturer-supplied 2D iterative software (Vue Point 2 D, GE Healthcare, USA; 2 iterations, 28 subsets, 3.27 slice thickness). A nuclear medicine specialist with comprehensive CT experience evaluated the cases to determine the localization and the degree of ^{18}F-FDG uptake. The images were interpreted as positive for infection when an area of increased tracer uptake was noted, either when higher than nearby muscle or when higher than healthy adjacent bone marrow tissue.

RESULTS

Overall, nine consecutive patients who underwent PET/CT to diagnose postoperative hardware-related spinal infection were included in the study. All the patients had undergone surgical treatment, with the index procedure taking place between January 1997 and October 2016. The four female and five male patients ranged in age from 26 to 75 years (mean age 59.2 ±16.4 years). The most common indication for surgery was spinal stenosis (n=3), followed by herniated lumbar disc (n=2) and lumbar vertebral fracture requiring fixation (n=2). Of the lumbar vertebral fractures, one followed trauma and the other was caused by a pathological fracture. Two additional patients underwent surgery for kyphosis and scoliosis. All patients underwent posterior spinal fusion. Average duration between the spinal surgery and the suspicion of infection was 34.1 months (range 0.4–204.7 months) [Table 1].

During the study period, eight patients had a single scan and one had two scans 3 months apart. An algorithmic strategy was applied using the PET/CT scan results to aid in the decision-making process. The patients were initially evaluated clinically via physical examination followed by laboratory tests, including complete blood count and differential as well as the inflammatory markers CRP and ESR. If the initial workup showed a clear-cut infection, the patient was treated accordingly. However, if the findings were inconclusive or raised a concern for a deep-seated infection around the hardware, a PET/CT was ordered. If the PET/CT findings supported an infection, surgical treatment was considered, unless the patient was not medically fit for surgery.

Four of the nine patients (patients 1–4) had initial PET/CT findings consistent with hardware-related infection [Figure 1]. In addition, patient 5 presented with findings indicating a superficial wound infection for which she underwent several debridement procedures. Hardware was retained. A PET/CT at that time did not show signs of deep-seated infection surrounding the hardware. Seven weeks later (a week after completing antibiotic treatment), the patient presented with sepsis and a repeat PET/CT demonstrated hardware-related deep spinal infection.

The PET/CT findings for four patients who presented with deep hardware-related infection, included intense pathological FDG uptake in the affected vertebras and disc space and increased FDG uptake in the adjacent paravertebral soft tissues adjacent to the hardware at multiple levels. An additional finding for two of the patients included FDG uptake at the bone and hardware interface of the interpedicular screws.

Among the five patients with PET/ CT scans with positive indications for a deep infection, four hardware-related infections were confirmed by positive tissue cultures (patients 1, 2, 3, and 5) and one by positive blood cultures (patient 4) [Table 1]. Patient 4, who presented a PET/CT positive for infection, did not have positive tissue cultures since he had positive blood cultures. The patient had a superficial wound infection 2 weeks after his spinal surgery. He was initially treated successfully with antibiotics; however, 5 months later, he presented with a

Table 1. Summary of patient characteristics, clinical and laboratory findings, PET/CT result, and microbiology tests

Patient number	Gender	Age, in years	Presenting symptoms	WBC*	CRP**	ESR***	Micro-organism from wound/ deep tissue	Extent of surgical fusion	Time between original fusion surgery and imaging, in months	Levels with increased uptake	SUV max at involved levels	PET/CT results	Additional imaging results	Further surgery	PET/CT result
1	Female	62	Pain	11.0	18.0	90	Pseudomonas	L2–S2	4.5	L2–L3	7.6	Bone and disc space distraction	CT scan: soft tissue adema under the area of the surgery, transverse fracture of L5 vertebral body	No	TP
2	Male	73	Pain and hardware failure	13.7	19.5	131	Serratia marcescens	T10–S2	0.4	L5–S2	8.6	Bone distraction, high uptake at vertebral implant interface, and corresponding paravertebral soft tissue thickening	None performed	Yes	TP
3	Female	26	Sepsis	13.0	NA	NA	Providencia suatii	L1–S2	22.2	L5–S1	25.6	Osteomyelitis and discitis, high uptake around L5 screw and in the soft tissue anterior to the vertebra	MRI: paravertebral findings around L5 without evidence of vertebral involvement. Gallium scan: signal in L3-L5	Yes	TP
4	Male	75	Wound complications	12.6	9.4	NA	Pseudomonas§	L3–L5	5.6	L3–L5 and sacroiliac joint	10.2	High uptake at the vertebral implant interface and in the right sacroiliac joint	MRI: discogenic changes at L4–L5, a collection is the soft tissue, prevertebral muscles, an inflammatory signal adjacent to the neural canal. Bone scan: increased signal at L4–L5	No	TP
5§§	Female	69	sepsis	12.0	21	NA	Pseudomonas, E. coli, and Acinetobacter	D11–L5	3.5	D9–D10	5.3	Postoperative changes, not indicative of infection	CT scan: non informative due to metal artifacts	No	FN → TP
6	Male	46	Pain	15.0	0.3	NA	None taken	L4–L5	7.8	None	2.5	Swollen soft tissue around laminectomy, assumingly scar tissue. Lumbar disc herniation. No pathologic uptake indicative of infection	CT scan: lumbar herniated disc. MRI: lumbar herniated disc	No	TN
7	Male	57	Wound complications	13.2	NA	NA	Negative	L4–L5	29.2	None	3.1	No pathological uptake	CT scan: non informative due to metal artifacts	No	TN
8	Female	50	Pain	12.1	3.1	NA	No cultures were obtained	L2–S1	204.7	None	3	No pathological uptake	MRI: Normal findings	No	TN
9	Male	75	Pain	6.8	5.5	40	No cultures were obtained	T10–sacrum	17.6	None	3.9	Postoperative changes, no pathological uptake in the spine, right upper lobe increase uptake.	MRI: degenerative changes in discs, bone irregularity at L4–L5, without bone edema or paravertebral inflammatory changes	No	TN

*WBC, normal range 4000–10,800 × 10^3/µl

**CRP, normal value < 0.5 mg/L

***ESR, normal values < 30 mm/hour

§Peripheral blood culture

§§Following a postoperative superficial infection treated with debridement, a first PET/CT was negative for deep hardware-related infection and after a course of antibiotics no further treatment was given. However, a week later the patient returned with sepsis and a recurrent PET/CT was positive. Positive tissue cultures followed

CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, FN = false negative, TN = true negative, TP = true positive, MRI = magnetic resonance imaging, PET/CT = positron-emission tomography/computed tomography, SUV = standardized uptake value, WBC = white blood cell count

recurrent infection and bacteremia with the previously isolated organism. A PET/CT demonstrated high ^{18}F-FDG uptake in the spine with implant interface [Figure 1].

Four patients had negative PET/CT findings. Patient 7 had a superficial wound infection following the index surgery. He presented again 29 months later with a wound complication. Inflammatory markers were elevated, yet wound cultures were negative. Following a negative PET/CT [Figure 2], conservative treatment with antibiotic therapy led to full resolution. Patient 8 had three additional spinal surgeries following his initial spinal laminectomy and fusion. He presented 11 years after the last surgery complaining of lumbar pain without elevated inflammatory markers. PET/CT and MRI results were not indicative of infection, cultures were not necessary, and treatment was not provided. Patient 9 underwent spinal fusion following a lumbar laminectomy complicated by infection. Due to persistent elevation of inflammatory markers he continued with suppression antibiotic treatment. The PET/ CT results did not demonstrate a spinal infection, but rather an increased uptake in the lung [Figure 3], thus no further treatment was given.

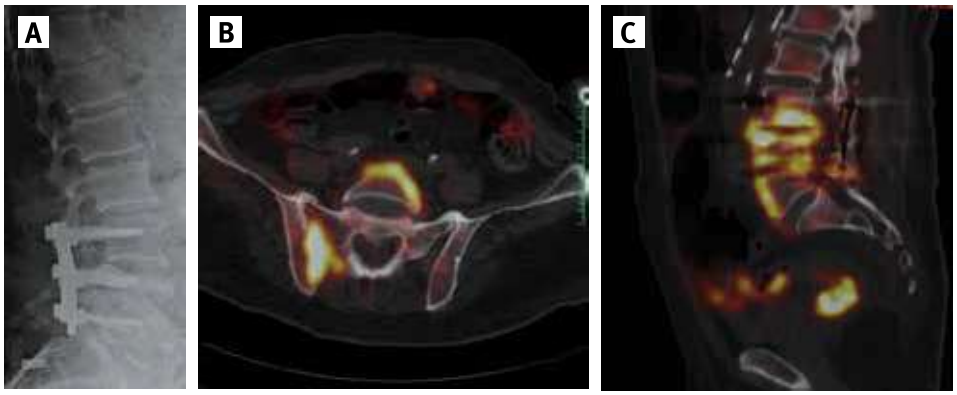

Figure 1. Initial PET/CT findings consistent with hardware-related infection obtained from patient 4
[A] Sagittal X-ray imaging, **[B]** PET/CT image, high uptake at the vertebra implant interface, **[C]** High uptake in the right sacroiliac joint

PET/CT = positron-emission tomography/computed tomography

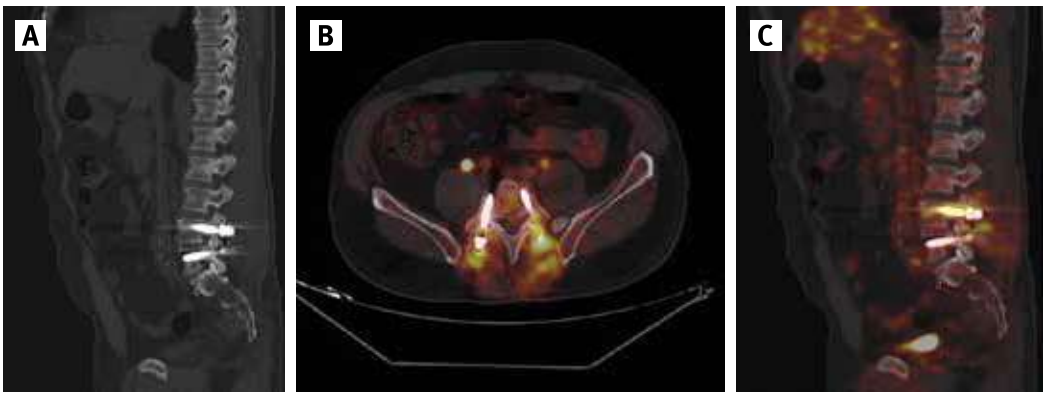

Figure 2. A sagittal CT image and a PET/CT image of patient 7. The PET/CT shows low uptake adjacent to the spinal hardware (white arrow)
[A] Sagittal CT imaging, **[B]** High uptake at the vertebra implant interface, **[C]** High uptake in the right sacroiliac joint

PET/CT = positron-emission tomography/computed tomography

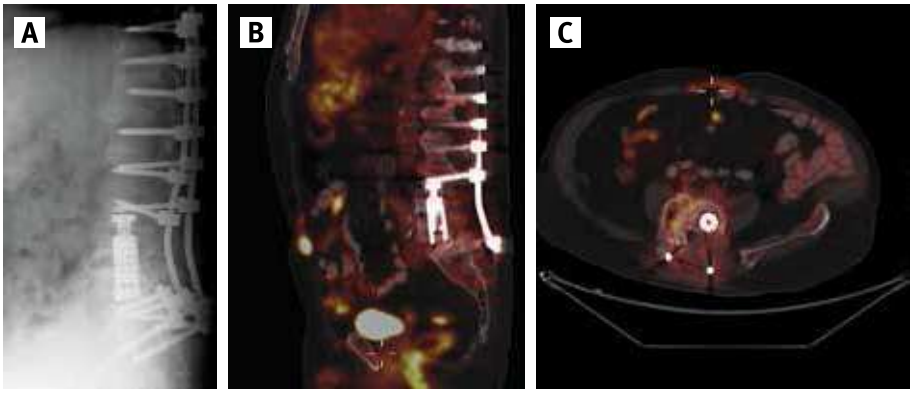

Figure 3. A sagittal X-ray imaging and a PET/CT image obtained from patient 9 shows postoperative changes with no pathological FDG uptake in the spine
[A] Sagittal X-ray imaging **[B]** High uptake at the vertebra implant interface. **[C]** High uptake in the right sacroiliac joint

PET/CT= positron-emission tomography/computed tomography, FDG = ^{18}F-fluorodeoxyglucose

Eight months after surgery patient 6 presented with worsening back pain and an increased WBC count of 15,000 (normal range 4000–10,800 × 103/µl. A workup for a possible infection around his hardware included a PET/CT that demonstrated normal scar tissue and a herniated disc at the level of L5–S1. Due to the PET/CT result, no further treatment for infection was provided and the patient continued with normal follow-up.

Of the five patients with positive PET/CT scans for a deep infection, two (22.2%) had spinal hardware removal/revision surgery following PET/CT. Patient 5 was not medically fit for surgery and was thus treated solely with antibiotics. Antibiotic treatment was successful for the remaining two patients, precluding the need for surgery.

DISCUSSION

Management of deep infection following instrumentation surgery of the spine is a medical challenge. While surgical irrigation and debridement combined with adjuvant antibiotic therapy are necessary, a controversy remains regarding retaining the hardware. Whereas the metal instrumentation may harbor bacteria and allow for biofilm formation, thus reducing the effectiveness of the antibiotic treatment, implant removal may be associated with pain, loss of stability, progressive deformity, and pseudoarthrosis [2,13]. In an effort to reduce the need for instrumentation removal, early diagnosis is essential.

Several diagnostic modalities are available for the diagnosis of postoperative hardware-related spinal infection, yet their effectiveness has not been determined. While X-rays and CT scans are widely available, they are not informative in the early stages of infection, and the diagnosis of deep infection might be overlooked [2,8]. Single-photon emission computed tomography (SPECT) is not sensitive enough for detecting adjacent soft tissue infections and may present abnormalities even after the infection has resolved, as subsequent bone remodeling continues. Supplementing the SPECT with gallium imaging can improve the specificity of the bone scan and speed up the diagnosis of the infection. However, the procedure necessitates the use of two tracers and the imaging sessions are long. Radiolabeled leukocyte (WBC) imaging was reported to be impractical for the diagnosis of spinal infections, partly due to increased uptake of labeled WBCs in normal hematopoietic active vertebral bone marrow [6,10]. MRI is currently considered the gold standard for the diagnosis of spinal infections [5]. It is highly affected by metal artifacts, and the differential diagnosis between degenerative inflammatory process and postoperative changes and infection can be problematic [1,10,12].

^{18}F-FDG PET/CT, initially used in the field of oncology, is emerging as a promising imaging modality for the diagnosis of hardware-related spinal infections. It possesses both metabolic and anatomic qualities and allows for early detection of the infection with high sensitivity and specificity. FDG uptake is especially high in activated immune cells, such as neutrophils and macrophages in the acute and chronic infection phases respectfully, as they present an increase in the expression and affinity of the GLUT glucose receptor [10]. Our results indicate 80% sensitivity, 100% specificity, and 88.9% accuracy (51.75%–99.72%). Few studies exist on the use of PET/CT for the diagnosis of hardware-related spinal infections. Schiesser and colleagues [11] reported on a subgroup of six patients with clinically suspected spinal implant infection in which PET/CT was used to rule out deep infection. In an additional series, 100% accuracy for PET/CT in the diagnosis of nine patients with suspected lumbar spine-related implant infection was reported [7]. PET/CT had 100% true positive results in the detection of infection in eight patients following spinal surgery with implants, whereas MRI imaging showed inconclusive results due to hardware-related artifacts. Following the PET/CT, all patients underwent surgery with hardware removal [12]. Finally, in a larger subgroup of 27 pediatric patients with suspected postoperative hardware-related spinal infection, the PET/CT was reported to have sensitivity, specificity, and accuracy of 100%, 81%, and 86%, respectively. While the negative predictive value was 100%, the positive predictive value was 65%, concluding that a negative PET/CT can be used to rule out infection, yet a positive test should be looked at with caution [6].

In our study, PET/CT was used for the diagnosis of nine patients with suspected hardware-related spinal infection. For eight of them previous imaging was available, four had results from CT scans, four with MRI results and two with Gallium scans. In the four patients with microbiologically confirmed deep infection, two CT scans were either non-informative or did not identify the deep infection. In an additional patient with multiple level infection, an MRI showed a single level paravertebral involvement, yet an additional bone scan supported the presence of infection.

LIMITATIONS

This study has several limitations. First, this is a retrospective case series with a relatively small number of patients. Nevertheless, since the current literature on this topic is lacking and consists only of small case series, we believe our results are informative regarding the use of PET/CT in these diagnostically challenging cases. Second, not all patients had additional imaging for comparison. Yet, as most of our treatment decisions were guided by the PET/CT results and eventually proved to be successful, we believe this method further substantiates the use of this imaging modality in this particular subgroup of patients.

CONCLUSIONS

PET/CT was found to be of high value in the diagnosis of postoperative hardware-related spinal infection, especially when other imaging modalities were uninformative or inconclusive. A positive scan dictated a more aggressive surgical

treatment and aided in the planning of the surgical intervention. Conversely, a negative scan led to a more conservative approach. Further prospective studies with a larger number of patients are warranted to evaluate the value of FDG PET in implant-related infections of the spine.

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Capsule

p53—still hazy after all these years?

The gene encoding the p53 tumor suppressor protein is the most frequently mutated gene in human cancer. Yet decades after the gene's discovery, the biology of cancer-associated missense mutations in p53 is still being debated. Previous studies have suggested that missense mutations confer tumor-promoting functions to p53. **Boettcher** and co-authors conducted a detailed analysis of p53 missense mutations in human leukemia, drawing on methodologies including genome editing, a p53 saturation mutagenesis screen, mouse models, and clinical. They found no evidence that p53 missense mutations confer an oncogenic gain of function. Rather, the mutations exerted a dominant-negative effect that reduced the tumor suppressor activity of wild-type p53.

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Eitan Israeli

Capsule

Driving HIV therapy forward

Almost 30 years ago, chimeric antigen receptor–modified (CAR) T cells, which are now associated with cancer therapy, were investigated as a treatment for human immunodeficiency viruses (HIV). Now, wielding new technology and biological knowledge, **Anthony-Gonda** et al. reported a series of multispecific anti-HIV CARs. These CARs targeted different portions of the HIV envelope protein and could eliminate diverse strains of HIV in vitro, even those that were resistant to potent broadly neutralizing antibodies. The CAR T cells were resistant to HIV infection themselves and could control HIV infection in a humanized mouse model. The persistent surveillance capabilities of CAR T cells provide hope that this therapy may one day help to eradicate HIV in infected individuals.

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Eitan Israeli

"We should not be simply fighting evil in the name of good, but struggling against the certainties of people who claim always to know where good and evil are to be found"

Tzvetan Todorov (born 1939), philosopher