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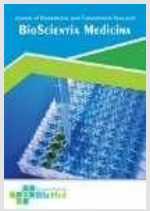

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The FAPI-FDG Mismatch: Unmasking an Occult Pancreatic Lesion via Fibroblast Activation Imaging Amidst Negative Glucose Metabolism and Morphological Findings

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A B S T R A C T

Background: Fibroblast activation protein inhibitor (FAPI) positron emission tomography (PET) has emerged as a promising modality for imaging the tumor microenvironment, specifically targeting cancer-associated fibroblasts (CAFs). While ^{18}F-FDG targets glucose metabolism, ^{68}Ga-FAPI targets stromal activation. Discrepancies between these modalities can offer unique insights into early pathogenesis. We report a rare case of incidental focal pancreatic uptake on ^{68}Ga-FAPI PET/CT in a patient with prostate cancer, occurring in the absence of metabolic activity on ^{18}F-FDG PET/CT or anatomical abnormalities on contrast-enhanced CT. **Case presentation:** A 75-year-old male with a history of acinar adenocarcinoma of the prostate (Gleason 7, post-TURP) underwent multimodal staging to evaluate for metastasis. 68Ga-PSMA PET/CT showed intermediate uptake in the prostate but no distant metastasis. Subsequent ^{68}Ga-FAPI-04 PET/CT revealed a striking, intense focal uptake in the pancreatic body. Conversely, follow-up ^{18}F-FDG PET/CT demonstrated physiological background uptake in the pancreas, and abdominal CT showed no pancreatic mass. Laboratory results indicated a slightly elevated CA 19-9 (45.6 U/mL). The findings present a diagnostic dilemma between early stromal-rich malignancy and focal inflammatory processes. **Conclusion:** This case highlights the FAPI-FDG Mismatch, suggesting that stromal remodeling may precede metabolic reprogramming and morphological changes in pancreatic lesions. ^{68}Ga-FAPI PET/CT demonstrates superior sensitivity for detecting occult stromal activity, necessitating new diagnostic algorithms for incidentalomas in the era of stromal imaging.

1. Introduction

The contemporary landscape of oncologic imaging is currently navigating a profound paradigm shift, moving away from an exclusive reliance on visualizing tumor cell metabolism and toward a more holistic characterization of the tumor microenvironment (TME).[1] For the past several decades, the cornerstone of this diagnostic framework has been ^{18}F-Fluorodeoxyglucose (^{18}F-FDG) Positron Emission Tomography/Computed Tomography (PET/CT). This modality revolutionized cancer staging by exploiting the Warburg effect, a fundamental metabolic reprogramming wherein malignant cells exhibit significantly upregulated glucose consumption and glycolysis, even under aerobic conditions.[2] By targeting the overexpression of glucose transporter 1 (GLUT1) and increased hexokinase activity in neoplastic cells, ^{18}F-FDG PET/CT became the gold standard for detecting viable tumor burden, monitoring treatment response, and identifying

metastatic dissemination.[3]

However, despite its entrenched status in clinical guidelines, ^{18}F-FDG imaging is not without significant limitations. Its diagnostic efficacy is inherently constrained by the biological heterogeneity of tumors and the physiological characteristics of surrounding tissues.[4] A primary limitation arises in malignancies that exhibit low cellularity, high mucin content, or slow proliferation rates, where the cumulative glucose demand is insufficient to generate a discernible signal above background noise. Furthermore, ^{18}F-FDG lacks specificity in anatomical regions characterized by high physiological glucose metabolism, most notably the brain, the myocardium, and the hepatopancreaticobiliary system. In the pancreas specifically, the intense physiological background uptake can obscure small or early-stage lesions, rendering FDG PET/CT less sensitive for the detection of occult pancreatic pathologies compared to other anatomical sites. These limitations have catalyzed the search for novel radiotracers that target alternative biomarkers independent of glucose metabolism, specifically those intrinsic to the structural architecture of the tumor rather than its metabolic throughput.[5]

Recent advances in cancer biology have illuminated the critical role of the tumor microenvironment, shifting the focus from the malignant seed to the fertile soil that sustains it. Central to this microenvironment are cancer-associated fibroblasts (CAFs), a heterogeneous population of activated stromal cells that orchestrate tumor progression, immune evasion, and therapeutic resistance. Unlike quiescent fibroblasts found in healthy tissue, CAFs are metabolically active and fundamentally alter the extracellular matrix (ECM) to favor invasion and metastasis. A defining surface marker of these activated fibroblasts is fibroblast activation protein (FAP), a type-II transmembrane serine protease. FAP is highly overexpressed on the cell surface of CAFs in more than 90% of epithelial carcinomas but is virtually absent in healthy adult tissues, making it an exquisite target for diagnostic imaging and potentially theranostics.[6] This differential expression profile has spurred the development of quinoline-based fibroblast activation protein inhibitors (FAPI) labeled with Gallium-68 (^{68}Ga). ^{68}Ga-FAPI PET/CT functions by binding directly to the active site of the FAP enzyme on the stromal fibroblasts, thereby visualizing the desmoplastic reaction rather than the tumor cells themselves. This mechanism offers a distinct advantage: because the tracer targets the stroma, which often occupies a larger volume than the tumor cells in certain cancers, it acts as a signal amplifier, rendering the tumor visible even when the malignant cell count is low.[7]

Nowhere is the potential of FAPI imaging more relevant than in the evaluation of pancreatic pathologies. Adenocarcinoma of the pancreas is biologically characterized by a dense, hypovascular desmoplastic reaction, a fibrotic fortress that can comprise up to 90% of the total tumor volume.[8] In this context, the actual malignant epithelial cells may represent only a minor fraction of the mass, contributing to the frequent failure of ^{18}F-FDG to detect early lesions. The desmoplastic stroma acts not only as a physical barrier to drug delivery but also as a metabolic modulator that may impair glucose delivery to the tumor core, further diminishing the FDG signal. Because ^{68}Ga-FAPI specifically targets this abundant stromal component, it is theoretically superior to metabolic imaging for the pancreas. FAPI PET/CT effectively lights up the desmoplasia, providing high-contrast images with exceptionally low background noise in the normal pancreatic parenchyma, which does not typically express FAP. This high tumor-to-background ratio (TBR) promises to redefine the detection limits for pancreatic lesions, potentially identifying malignancies at a stage when they are still amenable to surgical resection.

While the sensitivity of FAPI for desmoplasia is unrivaled, its specificity remains a subject of intense clinical scrutiny. Fibroblast activation is not a phenomenon exclusive to neoplasia; rather, it is a generic response to tissue injury and remodeling. FAP is significantly upregulated in a spectrum of benign

conditions, including chronic inflammation, wound healing, fibrosis, and autoimmune disorders such as IgG4-related disease. In the pancreas, chronic pancreatitis and focal autoimmune pancreatitis can induce a stromal reaction indistinguishable from the desmoplasia of malignancy on FAPI PET/CT.[9] This biological overlap creates a complex diagnostic landscape where a positive FAPI scan indicates the presence of activated fibroblasts but does not inherently confirm the presence of cancer cells. The interpretation of focal FAPI uptake in the pancreas, therefore, requires a nuanced understanding of the interplay between inflammation and neoplasia. Distinguishing between a benign inflammatory nodule and an early, potentially curable pancreatic carcinoma solely based on stromal intensity is becoming one of the most pressing challenges in nuclear medicine.[10]

This case report documents a compelling manifestation of these competing biological principles: the FAPI-FDG Mismatch. We present a detailed analysis of a 75-year-old patient with a history of prostate cancer who underwent multimodal staging. In this patient, ^{68}Ga-FAPI PET/CT revealed a striking, intense focal uptake in the pancreatic body. Crucially, this lesion was completely occult on standard contrast-enhanced CT, showing no mass effect or morphological abnormality, and was metabolically silent on ^{18}F-FDG PET/CT, exhibiting only physiological background uptake. This discordance presents a diagnostic conundrum. The intense FAPI signal suggests significant stromal remodeling or stromagenesis, a process often preceding the formation of a macroscopic tumor mass. Yet, the absence of glucose hypermetabolism and anatomical distortion defies the classical imaging features of malignancy. This scenario raises critical questions regarding the temporal sequence of tumorigenesis: does stromal activation precede metabolic reprogramming in pancreatic lesions? Or does this mismatch represent a benign fibro-inflammatory process masquerading as cancer in a high-risk oncologic patient?

The aim of this study is to elucidate the pathophysiological mechanisms driving isolated stromal activation in the absence of metabolic and morphological correlates, specifically challenging the reverse Warburg hypothesis in favor of a tumor-stroma ratio model. Furthermore, this report seeks to discuss the clinical implications of incidental FAPI findings in oncologic staging and to propose a pragmatic diagnostic algorithm for the management of FAPI-positive, FDG-negative pancreatic incidentalomas. The novelty of this work lies in the documentation of a distinct mismatch phenomenon that highlights both the superior sensitivity of FAPI for occult disease and the inherent specificity challenges that necessitate a new interpretive framework for molecular imaging.

2. Case Presentation

Written informed consent was obtained from the patient for the publication of this case report and any accompanying images. A 75-year-old male presented to the Department of Nuclear Medicine on May 28th, 2025, for a comprehensive metastatic evaluation. The patient's oncologic history commenced one month prior to the onset of obstructive lower urinary tract symptoms (LUTS), specifically a urinary frequency of six times daily and a significantly diminished urinary stream. These symptoms necessitated a therapeutic and diagnostic transurethral resection of the prostate (TURP) in April 2025. Histopathological analysis of the resected tissue confirmed a diagnosis of Acinar Adenocarcinoma of the prostate. The malignancy was stratified as intermediate risk, designated as Gleason Score 7 (Prognostic Grade Group 2, comprised of primary pattern 3 and secondary pattern 4) and World Health Organization (WHO) Grade 2. Furthermore, the specimen exhibited High-Grade Prostate Intraepithelial Neoplasia (HGPIN), indicating widespread field cancerization within the gland.

The patient's medical background was significant for chronic metabolic dysfunction, characterized by a 40-year history of dyslipidemia—manifesting as both hypercholesterolemia and hypertriglyceridemia—and

a 1.5-year history of hypertension. Family history was contributory, with documented Diabetes Mellitus and dyslipidemia in his father, suggesting a familial predisposition to metabolic syndrome. His current therapeutic regimen included androgen deprivation therapy (ADT) with Goserelin administered subcutaneously every three months, alongside cardiovascular management with Amlodipine 5mg, Candesartan 8mg, and Atorvastatin 20mg.

Physical examination revealed a patient in good general condition with stable hemodynamics, although a borderline elevated blood pressure of 146/77 mmHg was noted. Crucially, the abdominal examination was unremarkable; there were no palpable masses, hepatosplenomegaly, or tenderness to suggest gross intra-abdominal pathology (Table 1). Comprehensive laboratory analysis performed on June 24th, 2025, illustrated a complex biochemical profile. Renal function was preserved with a serum Creatinine of 0.64 mg/dL, facilitating contrast-enhanced imaging. The lipid profile remained deranged despite statin therapy, showing elevated Triglycerides (254 mg/dL) and low-density lipoprotein (LDL) at 124 mg/dL. In terms of tumor markers, the total prostate-specific antigen (PSA) was suppressed at 0.66 ng/mL, indicating a favorable response to ADT. However, the carbohydrate antigen 19-9 (CA 19-9) was found to be mildly elevated at 45.6 U/mL (Reference range: <37 U/mL). This biochemical outlier, occurring in an asymptomatic patient, provided the initial signal for potential pancreatobiliary pathology.

TABLE 1. SUMMARY OF ANAMNESIS, GENERAL EXAMINATION, LABORATORY ASSESSMENT, AND DIAGNOSIS

Clinical Parameter & Patient Data	
1. PATIENT PROFILE & ANAMNESIS	
Patient Demographics	Male, 75 years old
Chief Complaint	Lower Urinary Tract Symptoms (LUTS): Frequency (6x/day), weak stream, intermittent flow. Duration: 1 month.
History of Present Illness	Post-TURP (April 2025) for Carcinoma Prostate. No dysuria, no hematuria, no perineal pain. Occasional right abdominal pain associated with triglyceride spikes.
Comorbidities	Hypercholesterolemia & Hypertriglyceridemia (40 years), Hypertension (1.5 years).
Medications	Goserelin (Zoladex 3-monthly), Amlodipine 5mg OD, Candesartan 8mg OD, Atorvastatin 20mg OD.
Social History	Diet rich in coconut milk, fried foods, instant noodles. Non-smoker, Non-drinker.
2. PHYSICAL & GENERAL EXAMINATION	
General Status	Good condition (ECOG 0), Compos Mentis. BMI: 28.0 kg/m² (Wt: 80kg, Ht: 169cm).
Vital Signs	BP: **146/77 mmHg** | HR: 71 bpm | RR: 18/min | Temp: 36.8°C | SpO2: 99%
Head & Neck	Conjunctiva non-anemic, Sclera non-icteric.
Thorax	Heart: S1/S2 normal, no murmurs. Lungs: Vesicular breath sounds, no rales/wheezing.
Abdomen	Soft, flat, bowel sounds normal. No palpable hepatosplenomegaly on physical exam (Note: Hepatomegaly present on CT). Slow skin turgor.
3. LABORATORY & HISTOPATHOLOGY ASSESSMENT	
Histopathology (Prostate)	Acinar Adenocarcinoma, **Gleason Score 7 (3+4)**, WHO Grade 2, with High-Grade PIN.
Tumor Markers	PSA Total: 0.66 ng/mL (Suppressed post-ADT) CA 19-9: **45.6 U/mL** (Ref: <37 U/mL)
Lipid Profile	Total Cholesterol: 194 mg/dL HDL: **31 mg/dL** (Low) LDL: **124 mg/dL** (High) Triglycerides: **254 mg/dL** (High)
Renal Function	Ureum: 23.4 mg/dL | Creatinine: 0.64 mg/dL (Normal).
4. WORKING DIAGNOSIS	
Primary Diagnosis	**Prostate Acinar Adenocarcinoma** (Post-TURP, under ADT).
Incidental Findings	1. **Occult Pancreatic Lesion** (^{68}Ga-FAPI Positive / ^{18}F-FDG Negative / CT Occult). 2. Dyslipidemia (Mixed Hyperlipidemia). 3. Hypertension.

A sequential multimodal imaging protocol was executed to comprehensively evaluate metastatic dissemination, utilizing a GE Discovery MI DR PET/CT system. Initial staging commenced on May 28th, 2025, with ^{68}Ga-PSMA PET/CT, which delineated intermediate radiotracer avidity within the prostatic gland (Primary Score 2), corroborating the known malignancy (Figure 1). Significantly, this examination confirmed locoregional containment, with a distinct absence of PSMA-expressing lymphadenopathy or distant metastases to the skeletal system or viscera.

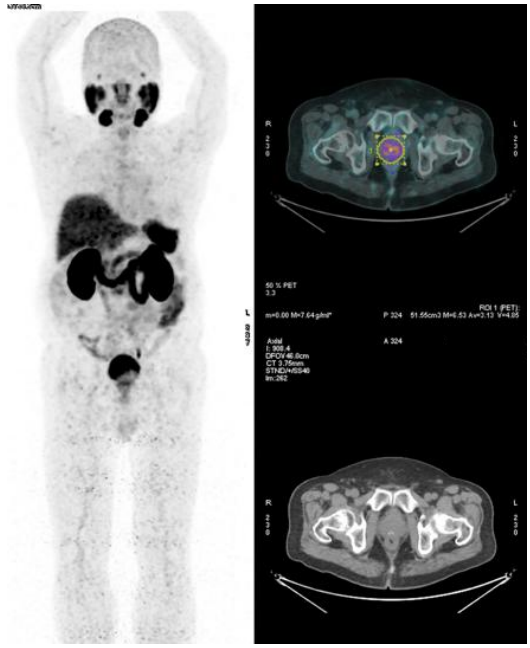

Figure 1. ^{68}Ga-PSMA PET/CT.

Subsequently, to assess stromal involvement, the patient underwent ^{68}Ga-FAPI-04 PET/CT on June 4th, 2025 (Figure 2). While the primary prostatic lesion demonstrated minimal fibroblast activation—suggestive of a low burden of cancer-associated fibroblasts—the scan unmasked a striking incidental finding. An intense, focal accumulation of the tracer was identified in the pancreatic corpus, quantified with a standardized uptake value (SUVmax) of 7.8 and a tumor-to-background ratio of 6.5. This stromal hotspot was an isolated phenomenon, with no other FAPI-avid lesions detected systemically.

To investigate morphological correlates, a Contrast-Enhanced CT of the abdomen was performed on June 25th, 2025. Although the scan visualized the primary prostatic mass with calcifications infiltrating the posteroinferior bladder wall, the pancreas appeared structurally unremarkable. There was no evidence of a space-occupying lesion, ductal dilatation, or peripancreatic stranding to explain the FAPI avidity. The diagnostic conundrum was further compounded by ^{18}F-FDG PET/CT imaging on July 22nd, 2025 (Figure 3). While the prostate exhibited expected hypermetabolism consistent with aggressive carcinoma, the pancreatic corpus remained metabolically silent. The region corresponding to the FAPI-avid lesion demonstrated a background SUVmax of 1.8, indistinguishable from physiological parenchyma. Collectively, these findings characterized a discordant incidentaloma: a lesion defined by high stromal activity (FAPI-positive) yet devoid of macroscopic mass effect (CT-negative) or accelerated glucose metabolism (FDG-negative).

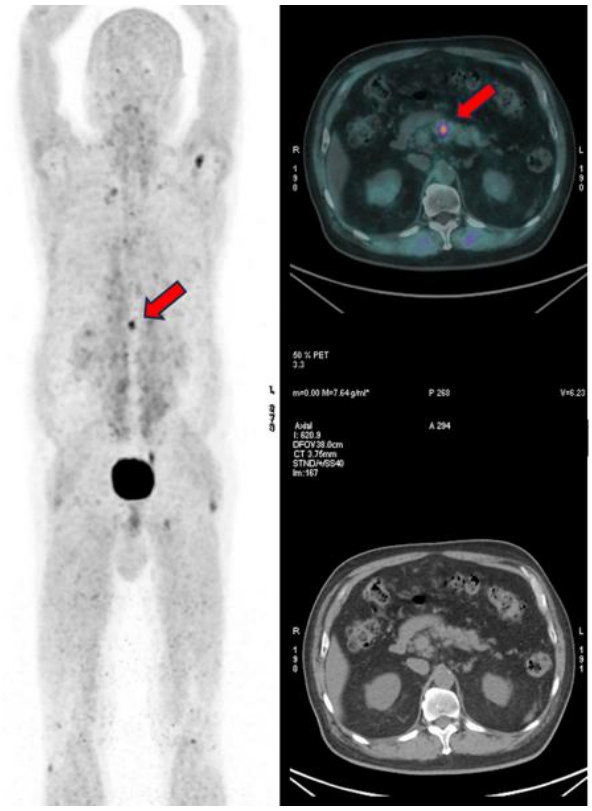

Figure 2. ^{68}Ga-FAPI PET/CT.

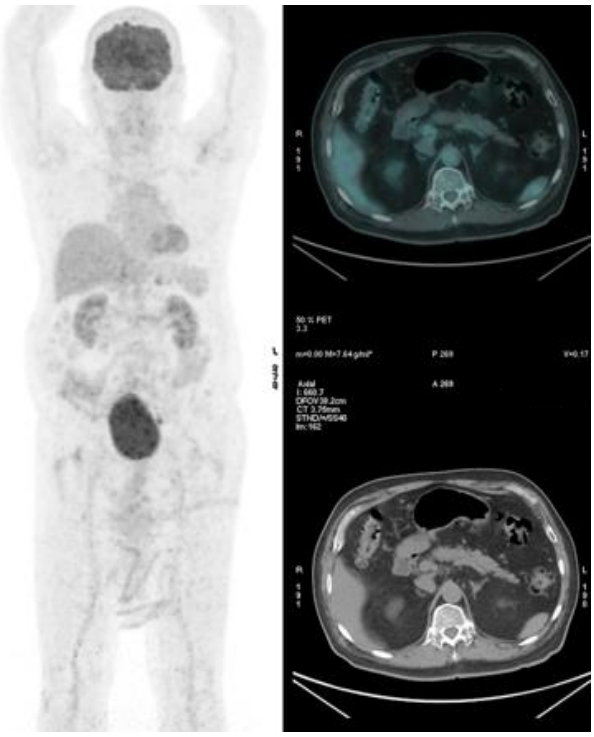

Figure 3. ^{18}F-FDG PET/CT.

3. Discussion

This case exemplifies a complex and increasingly relevant diagnostic scenario introduced by the emergence of fibroblast activation protein inhibitor (FAPI) PET/CT: the identification of stromal-dominant lesions that remain invisible to conventional metabolic and anatomical imaging modalities. The patient presented with a clear history of prostate carcinoma, yet the pivotal finding was an incidental, intense focal uptake in the pancreatic body detected solely by ^{68}Ga-FAPI-04. The complete discordance between this finding and the negative results from ^{18}F-FDG PET/CT and contrast-enhanced CT constitutes a FAPI-FDG Mismatch. This phenomenon challenges traditional oncologic imaging paradigms, which rely heavily on glucose metabolism and morphological mass effect. The following discussion dissects the pathophysiological mechanisms underlying this mismatch, the diagnostic dilemma between early malignancy and benign fibro-inflammatory conditions, and the clinical implications of occult stromal activity.[11]

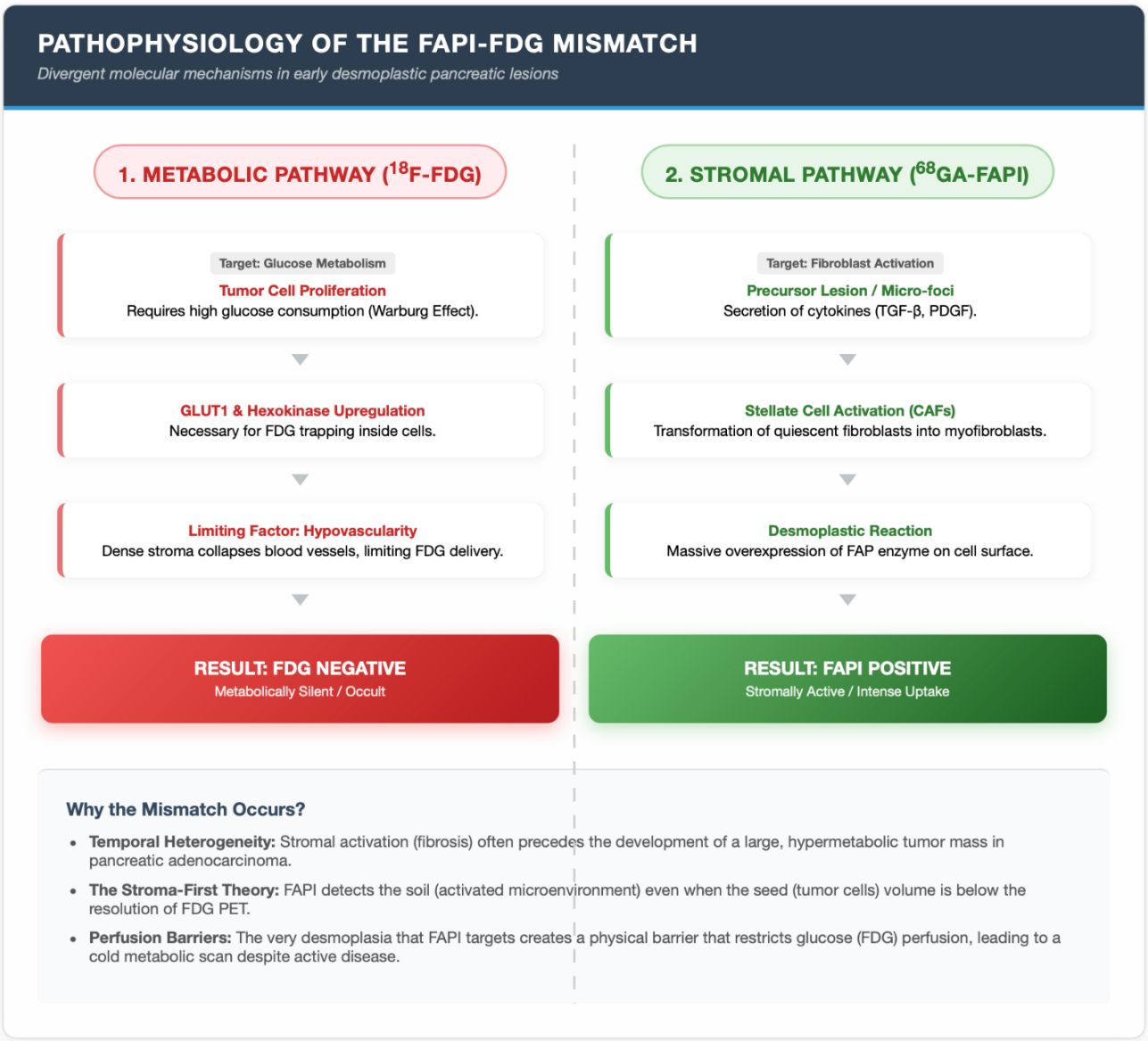

Figure 4. Pathophysiology of the FAPI-FDG mismatch.

The divergent retention patterns of ^{68}Ga-FAPI and ^{18}F-FDG observed in this case can be elucidated by analyzing the temporal and biological heterogeneity of pancreatic tumorigenesis.[12] The utility of ^{18}F-FDG PET/CT in oncology is predicated on the Warburg effect, a metabolic reprogramming wherein malignant cells exhibit upregulated expression of glucose transporter 1 (GLUT1) and increased hexokinase activity to support rapid proliferation via aerobic glycolysis (Figure 4). Consequently, FDG imaging visualizes the aggregate metabolic volume of viable tumor cells. However, this modality has inherent limitations in pancreatic adenocarcinoma (PDAC), particularly in early-stage lesions or those with a low fraction of neoplastic cells relative to the total tumor volume. In stark contrast, ^{68}Ga-FAPI does not target the neoplastic cells directly, but rather the fibroblast activation protein (FAP) expressed on the cell surface of cancer-associated fibroblasts (CAFs). In the context of pancreatic pathology, the recruitment and activation of fibroblasts are often the initiating events in the disease process.[13] Driven by paracrine signaling involving cytokines such as transforming growth factor-beta (TGF-beta) and platelet-derived growth factor (PDGF) secreted by microscopic precursor lesions or early tumor foci, quiescent fibroblasts transition into an activated myofibroblastic phenotype. This activation results in the vigorous deposition of extracellular matrix components, creating a dense, desmoplastic stroma.[14]

The FAPI-FDG Mismatch in this patient likely signifies a lesion in a stromal-dominant phase. The intense FAPI uptake (SUVmax 7.8) reflects a robust desmoplastic reaction. The concurrent lack of FDG uptake can be explained by two primary hypotheses.[15] First, the dense collagenous stroma characteristic of PDAC generates high interstitial fluid pressure, which collapses microvasculature and induces hypoperfusion. This physical barrier may impair the delivery of the FDG radiotracer to the neoplastic cells, rendering the lesion metabolically cold despite being biologically active. Second, the mass of the actual malignant epithelial cells may be below the spatial resolution of the PET scanner, while the volume of the activated stroma—which can constitute up to 90% of the tumor mass—is sufficient to produce a strong FAPI signal.

Furthermore, this mismatch may illustrate a reverse Warburg effect. In this metabolic model, CAFs undergo aerobic glycolysis and secrete energy-rich metabolites, such as lactate and pyruvate, which are then taken up by adjacent cancer cells to fuel mitochondrial oxidative phosphorylation. In such a scenario, the stromal cells (CAFs) would be the primary metabolizers of glucose. However, if the specific timeframe of the scan captures a phase where fibroblast activation (FAP expression) is the dominant molecular event outpacing glucose consumption, or if the specific CAF sub-population expresses FAP intensely without high GLUT1 levels, the result is a FAPI-positive/FDG-negative discordance. Thus, the scan effectively unmasks cellular machinery that precedes the classic hypermetabolic state associated with advanced malignancy.[16]

The detection of FAP expression is a sensitive indicator of tissue remodeling, but it lacks absolute specificity for malignancy.[17] FAP is significantly upregulated in any pathological condition involving fibroblast activation, including wound healing, chronic inflammation, and fibrosis. Therefore, distinguishing between an early-stage pancreatic carcinoma and a benign fibro-inflammatory process is the central challenge in this case.

The association between high FAP expression and pancreatic adenocarcinoma is well-established, with histopathological studies confirming FAP presence in over 90% of PDAC cases.[18] The intensity of FAPI uptake often correlates with the aggressiveness of the desmoplastic reaction, which is a prognostic marker for poor survival and lymph node metastasis. Previous studies comparing FAPI and FDG have consistently demonstrated that FAPI detects more pancreatic lesions than FDG, with higher tumor-to-background ratios. In this patient, the focal nature of the uptake in the pancreatic body is concerning for a neoplastic etiology. While FDG was negative, the sensitivity of

FDG for small, non-mass-forming pancreatic tumors is notoriously low (approximately 50-70%), whereas FAPI has shown sensitivities approaching 97-100% in various cohorts.

Quantitative assessment utilizing the Maximum Standardized Uptake Value (SUVmax) has been proposed as a method to stratify risk.[19] A prospective study by Röhrich et al. suggested a specific cutoff SUVmax of 10.2 to differentiate malignant from benign pancreatic lesions, achieving a sensitivity of 95% and specificity of 80%. Our patient presented with an SUVmax of 7.8. This value falls into an intermediate or equivocal zone. It is below the high-probability threshold for advanced malignancy but significantly above the background activity (TBR 6.5), and within the range (3.1–9.1) previously described for benign conditions in retrospective analyses. This intermediate intensity prevents a definitive rule-out of malignancy, as early-stage or low-grade tumors may not yet have achieved the maximal stromal density seen in advanced disease.

The differential diagnosis must include IgG4-Related Disease (IgG4-RD) and focal chronic pancreatitis. IgG4-RD is a systemic autoimmune condition characterized by lymphoplasmacytic infiltration and storiform fibrosis.[20] Case reports have documented intense FAPI uptake in the pancreas of patients with active IgG4-RD, often exceeding the uptake of FDG. Given the patient's age (75 years) and history of dyslipidemia, an autoimmune or inflammatory etiology is plausible. However, IgG4-RD typically presents with diffuse organ involvement (autoimmune pancreatitis), biliary strictures, or salivary gland involvement, none of which were observed in this patient. Similarly, chronic pancreatitis can manifest as focal fibrosis mimicking cancer. Uptake of FAPI in chronic pancreatitis is attributed to the activation of pancreatic stellate cells, the resident fibroblasts responsible for fibrosis. The patient was asymptomatic, denying abdominal pain or steatorrhea, which makes active acute pancreatitis unlikely, but does not exclude asymptomatic focal fibrosis or groove pancreatitis. The laboratory findings add another layer of complexity. The patient's CA 19-9 level was 45.6 U/mL, which is mildly elevated above the reference range of 37 U/mL. While CA 19-9 is the standard biomarker for pancreatic cancer, it has limited specificity and can be elevated in benign cholestasis, pancreatitis, or even dyslipidemia. However, the combination of a focal FAPI-avid lesion and an elevated CA 19-9, even in the absence of a CT mass, raises the pre-test probability of early malignancy significantly higher than if the biomarker were normal.

The most radiologically significant aspect of this case is the absence of a morphological correlate on contrast-enhanced CT (CECT). The pancreas appeared normal in size and shape, with no definition of a mass, ductal dilation, or vascular encasement. In conventional oncology, the absence of a mass often leads to a watch and wait approach. However, the advent of FAPI PET/CT necessitates a re-evaluation of this dogma. FAPI PET/CT has been demonstrated to redefine the Gross Tumor Volume (GTV) by detecting cellular infiltration that extends well beyond the anatomical borders visible on CT or MRI. This suggests that molecular volume (the extent of stromal activation) exceeds morphological volume (the structural distortion of tissue). In this case, the FAPI signal acts as a beacon for molecular fibrosis or early stromal organization that precedes the formation of a macroscopic tumor mass.[17,18]

This finding aligns with the stroma-first hypothesis in pancreatic carcinogenesis. If the desmoplastic reaction is an early event induced by precursor lesions like pancreatic intraepithelial neoplasia (PanIN), FAPI PET could theoretically serve as a screening tool for pre-invasive or micro-invasive disease. The literature supports this, with studies identifying incidental FAPI uptake in patients undergoing scanning for other indications; while a subset of these are benign, others represent occult malignancies missed by standard protocols. Therefore, a CT-negative status should not reassure the clinician in the face of strong, focal FAPI avidity. The FAPI-positive/CT-negative status may represent the elusive window of opportunity for

curative resection in pancreatic cancer, a disease typically diagnosed only after mass effect and vascular invasion have rendered it unresectable.

The primary limitation of this case report is the absence of histopathological confirmation of the pancreatic lesion. Despite the concerning imaging features, the patient was asymptomatic, and the risks associated with invasive pancreatic biopsy (such as post-procedure pancreatitis, bleeding, or perforation) were deemed to outweigh the immediate benefits given the uncertainty of the diagnosis. Consequently, the final diagnosis remains presumptive based on multimodal imaging rather than definitive cytology. This reflects a common real-world clinical dilemma: how to manage incidentalomas detected by novel, highly sensitive molecular imaging agents.[19,20]

This limitation highlights the urgent need for future research to establish standardized management algorithms for FAPI-avid incidental findings. Large-scale, prospective cohorts with mandatory pathological correlation are required to refine the SUVmax thresholds that distinguish benign fibrosis from desmoplastic malignancy. Furthermore, the utility of dual-time-point imaging should be explored. Preliminary data suggest that uptake in inflammatory lesions tends to wash out or decrease on delayed scanning (3 hours post-injection), whereas malignant lesions, driven by continuous CAF activity and tracer retention, demonstrate stable or increasing uptake. Implementing such protocols could non-invasively improve the specificity of FAPI PET/CT in equivocal cases like this one. Additionally, longitudinal follow-up of this patient is essential. If the lesion is indeed an early malignancy, morphological changes or metabolic evolution (becoming FDG-positive) may occur over time. If it remains stable, a benign etiology such as focal fibrosis becomes more likely. The integration of FAPI PET/CT into routine staging for non-pancreatic cancers (like prostate cancer) will likely increase the frequency of such incidental findings, making the development of interpretation guidelines a priority for the nuclear medicine community.

4. Conclusion

This case reports a compelling and instructive instance of a ^{68}Ga-FAPI-positive, ^{18}F-FDG-negative, and CT-occult focal pancreatic lesion in a patient with prostate cancer. The findings underscore a critical evolution in oncologic imaging: the shift from detecting the metabolic consequences of cancer (glycolysis) to visualizing the structural and supportive microenvironment (stromal activation) that facilitates tumor growth. The intense focal uptake of FAPI in the absence of glucose hypermetabolism or anatomical mass effect suggests that fibroblast activation and stromal remodeling may be the earliest detectable molecular events in pancreatic pathology, preceding both metabolic reprogramming and morphological distortion. While the FAPI-FDG Mismatch highlighted in this case demonstrates the superior sensitivity of ^{68}Ga-FAPI for detecting occult stromal-rich lesions, it simultaneously presents a diagnostic challenge regarding specificity. The overlapping FAPI avidity profiles of early desmoplastic carcinoma and benign conditions like IgG4-related disease or focal fibrosis create a grey zone for interpretation. In cases of intermediate FAPI uptake (SUVmax ~7-8) without metabolic or anatomical correlation, clinicians must navigate a complex decision matrix, carefully weighing the possibility of a potentially curable, occult malignancy against the risks of invasive investigation for benign disease. Ultimately, this case advocates for the incorporation of FAPI PET/CT as a complementary tool in difficult diagnostic scenarios, particularly for hypovascular or stromal-dense tumors. It also serves as a call to action for the medical community to develop robust, evidence-based criteria for the management of FAPI-avid incidentalomas. As molecular imaging continues to advance, our ability to detect the seeds of cancer in the stroma before the soil is visibly disrupted offers a promising new frontier for early diagnosis and improved patient outcomes.

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