

Online Resource 1: Case descriptions

¹⁸F-fluoro-ethyl-tyrosine PET co-registered with MRI in patients with persisting acromegaly

PITUITARY

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GROUP 1 (fig. 3 and 4)

Case 2 (fig. 3): A 40-year-old male was diagnosed with acromegaly in 2019 (IGF-1 at +10 SD, with relatively low GH levels, nadir 1.7 ug/L) due to a small macroadenoma located ventrally in the left sella in close proximity to, but with no visible invasion of, the cavernous sinus. Accordingly, complete surgical resection with full clinical and biochemical remission was anticipated. He underwent pituitary surgery (with positive histology), resulting in improved biochemistry (IGF-1 between +3 and +4 SD and undetectable GH (< 0.07 mcg/L) during suppression test), but with persistent and worsening clinical symptoms (intractable headache and fatigue) in the months after surgery. His symptoms, combined with increasing IGF-1 levels up to +4.1 SD (average +3.5) led to the initiation of medical treatment which resulted in clinical and biochemical improvement. Postoperative MRI was difficult to interpret due to postoperative changes, showing initially no clear remnant but subtle changes in the postoperative region adjacent to the cavernous sinus. A tumor remnant was suspected and, in view of progressive worsening of the patient's symptoms, reappraisal of surgical possibilities was considered a priority. To optimize the outcome of revision surgery, FET-PET/MRI^{CR} was performed and showed asymmetrical tracer accumulation in the sella with higher uptake left laterally. An additional axial MRI was performed for better fusion with FET-PET images, which revealed a less enhancing lesion medial to the left carotid artery, at the site of increased tracer uptake, suggestive for residual tumor. Re-exploration was advised with an extended, bony resection to expose the carotid artery.

TSS was performed with a possibly estimated chance for remission. The surgeon removed the medial cavernous sinus wall and took biopsies of the region without detecting clear adenoma tissue. Perioperative findings and histology were negative, e.g. normal pituitary tissue and fibrosis. Postoperative, symptomatology improved markedly, but biochemistry did not change significantly (glucose-mediated suppression of GH remained normal (undetectable GH (< 0.07 mcg/L)) and although IGF-1 levels were reduced they remained modestly increased but stable (+2.9 SD, 1.45x ULN)). The postoperative scan showed that the suspected lesion was removed. No additional treatment has been recommended up to the last follow-up visit (at 22 months). From a surgical perspective the IOQ for this case is an IOQ-3 (remission not achieved, no permanent complications). Given his clinical improvement without need for medication, the IOQ from a patient perspective could be considered as an IOQ-1.

Given the biochemical outcome, the contribution of FET-PET/MRI^{CR} in this patient is limited. We proceeded to surgery in an early state where biochemistry was not yet very clear because of severe symptomatology. The indication for FET-PET/MRI^{CR} was correct though (to optimize outcome of revision surgery).

Case 3 (fig. 3): A 23-year-old female, diagnosed in 2020 with a GH secreting macroadenoma (with suprasellar extension but not cavernous sinus invasion) was operated once (positive histology), with persistent clinical and biochemical disease for which she was treated with pegvisomant, but experienced severe side effects. On postoperative MRI, a suspected remnant on the sellar floor was difficult to distinguish from postoperative changes. To make a better distinction a FETPET-MRI^{CR} was performed. Tyrosine uptake was consistent with conventional imaging, with a suspected lesion on the sellar floor, extending to the sphenoidal sinus. Clinical and biochemical remission was considered possible and complication risk low; hence the patient was counselled for a revision TSS. Centrally and left in the sella, macroscopic tissue suggestive of adenoma, corresponding to FET-PET/MRI^{CR}, was resected with positive histology. No complications occurred. She is currently in biochemical remission with improvement in clinical symptoms (IOQ-1). In this young woman with a not well understood outcome of first TSS based on initial MRI, and a difficult to interpret postoperative MRI due to postoperative changes, FET-PET/MRI^{CR} helped optimize the outcome of a revision TSS.

Case 4 (fig. 3): A 32-year-old female patient, diagnosed with acromegaly in 2018, due to a pituitary (large) microadenoma on the left in close proximity to the cavernous sinus, but without clear invasion, was operated twice (both with positive histology, second TSS Ki67 of 5%, no remission achieved). Between the first and second TSS she was treated with SRL on which she experienced side effects. Because of mildly active disease with distressing symptoms, treatment with pegvisomant was initiated several months after the second TSS, with a positive effect but incomplete disease control (persistent symptoms, mildly increase IGF-1). On conventional MRI a small left sellar residue was suspected but difficult to distinguish from postoperative changes. Hence a FET-PET/MRI^{CR} was performed to confirm the pathological activity in this area. Tyrosine uptake was consistent with the findings on the MRI. Achieving biochemical remission with a third procedure was estimated as possible. Perioperative findings were positive and concordant with imaging, and histology was confirmative. In the postoperative course, she was readmitted because of hyponatremia due to SIADH. Currently, she is in biochemical remission (GH nadir after glucose load < 0.4 ug/L and normalized IGF-1) with corresponding clinical improvement (IOQ-1). In this patient with a not completely understood outcome of the second surgery, although there was a close relationship with the cavernous sinus from diagnosis, and a difficult to interpret postoperative MRI due to postoperative changes, FET-PET/MRI^{CR} aided in optimizing the outcome of third surgery.

Case 6 (fig. 4): A 50-year-old male patient was diagnosed with acromegaly due to a macroadenoma without cavernous sinus invasion in 2019. He had pituitary surgery twice (both surgeries with confirmative histology, but persistent disease; second surgery MET-PET/MRI^{CR} guided) and was treated with pegvisomant between both surgeries and from 6 months after the second one. Both postoperative outcomes were not well understood based on retrospective assessment of the baseline images. Despite improved biochemical control on medication, he still had persistent disease. Conventional postoperative MRI was suspicious for a residue on the sella floor from the midline to the left without cavernous sinus invasion. FET-PET/MRI^{CR} was performed to confirm this was an active lesion and showed clear asymmetry on the left anterolateral side of the sella. Of note, the findings of the previous MET-PET/MRI^{CR} and current FET-PET/MRI^{CR} were concordant.

Total resection was considered possible and TSS was performed. Macroscopic residues were obtained from both suggested areas on MRI and FET-PET/MRI^{CR}, both with positive histology. No complications occurred. He experienced clinical improvement, with improved biochemistry (GST 0.57 ug/L; IGF-1 +3.6 SD) and some volume reduction at the site of preoperatively identified lesion on postoperative MRI (IOQ-3). At last follow up visit, almost 2 years postoperative, pegvisomant was restarted in a low dose because of slight increase in symptoms possibly related to the, still stable, increased IGF-1, with a positive effect. In this patient with an unexplained outcome of previous surgeries based on initial imaging and perioperative findings, FET-PET/MRI^{CR} provided valuable extra information in confirming an active lesion.

Case 9 (fig. 3): A 54-year-old female patient was diagnosed with acromegaly in 2020 (macroadenoma, no cavernous sinus invasion) and was operated twice elsewhere, the first surgery in 2021 with positive histology and the second surgery because of persistent disease in 2022 with negative histology. She was treated with SRL before the first (5 months) and second (duration unknown) surgery, with side effects (gastrointestinal and gallbladder symptoms). She was referred to our center because of persistent disease with increasing IGF-1 and progressive symptoms, but no clear remnant on MRI due to postoperative changes. The estimated remission chance of both previous surgeries was retrospectively estimated as likely. FET-PET/MRI^{CR} was performed to locate the culprit lesion and showed increased tracer uptake on the left cranially of the resection cavity and a small spot on the right side next to the cavernous sinus. Total resection was considered possible with low estimated complication risk and a third TSS was performed. Surgery was difficult because of scar tissue, both left (most convincing) and right possibly abnormal tissue was resected. Histology was positive for both sides. No complications occurred. Biochemical remission was achieved, and clinical symptoms

improved (IOQ-1). In this patient with persistent disease after 2 surgeries despite a likely estimated remission chance, and no clear remnant lesion on MRI due to postoperative changes, FET-PET/MRI^{CR} was used to optimize outcome of a third surgery.

GROUP 2 (fig. 5 and 6)

Case 1 (fig. 5): A 57-year-old male was diagnosed with acromegaly in the nineties, for which transsphenoidal surgery was performed thrice (1st and 3rd TSS positive histology, 2nd TSS negative histology). No MRI-scan at diagnosis was available. Because of persistent disease he was treated with SRL and pegvisomant for already 21 years. At presentation in our center, he was insufficiently controlled both clinically and biochemically under maximum tolerable medication dose (IGF-1 +3.6 SD). On MRI a possible residue was seen in the right sellar region, with uncertain cavernous sinus invasion. FET-PET/MRI^{CR} was performed to confirm the activity at this location and to differentiate from postoperative changes. Tracer uptake was consistent with the conventional MRI, suggesting a residue on the right side of the sella, just next to the cavernous sinus. A 4th TSS was considered useful, intended to reduce medication dose and radiation field if needed (possibly), relieve symptoms (possibly), and perhaps even biochemical remission (unlikely), with a moderate risk of further pituitary insufficiency (AVP deficiency) and CSF leak. Surgical findings were consistent with imaging, but pituitary adenoma was unclear on pathology exam (multiple hormone positivity). No complications occurred. The patient experienced clinical improvement, and improved biochemical control with only pegvisomant which was restarted 3 months postoperative, and fractionated radiotherapy was performed 6 months postoperative as was anticipated (IOQ-1). No clear postoperative remnant was visible on MRI.

FET-PET/MRI^{CR} was considered as added value in a high need patient with a difficult to interpret MRI and no initial MRI at diagnosis, to assess all feasible options and to avoid an unnecessary intervention in advance.

Case 5 (fig. 6): A 57-year-old male was diagnosed in 2012 with acromegaly due to a macroadenoma, extending supra- and parasellar with left cavernous sinus extension (Knosp 3A). He was operated once followed by combined medical treatment for persistent disease (lanreotide, later pasireotide, then pegvisomant). At the time of presentation to our center, acromegaly was insufficiently controlled, with suboptimal quality of life, despite maximal tolerable medical treatment, therefore urging the need for alternative treatment. Four possible residues were visible on the conventional MRI –

ventrolateral to the left, just below the carotid (lesion 1); between the carotids on the left side (lesion 2), caudal to the chiasm against the pituitary stalk (lesion 3), and paramedial left in the sella most suspicious for resection cavity (lesion 4). FET-PET/MRI^{CR} was performed to optimally map surgical options, showing increased uptake in the left cavernous sinus between the horizontal parts of the cavernous sinus segment of the carotid artery (lesion 2 on MRI), without uptake in the other areas. Re-exploration of all possible lesions on MRI including intradurally (next to stalk) was proposed, for debulking to reduce medication (estimated as possible). Total resection was considered unlikely. Both left sellar and supradiaphragmatic tissue originating from the left part of the pituitary stalk was removed (lesions 4 and 3, respectively), with histopathological confirmation of the latter (lesion 3 on MRI). Lesion 2 on MRI was surgically inaccessible. Postoperative course was complicated by CSF leakage necessitating a temporary ELD. Clinical improvement was achieved, GH normalized (GH nadir 0.37 ug/L) and IGF-1 at last follow up (almost 2 years postoperative) was +3.3 SD without any medical treatment (IOQ-1). Postoperative MRI showed a small possible remnant intradural next to the pituitary stalk. In this patient with longstanding medical treatment with a high need for alternative treatment because of suboptimal quality of life despite maximal medical treatment, with multiple possible foci on MRI, FET-PET/MRI^{CR} was helpful for mapping surgical targets. Although a FET-PET-negative lesion was found to be histologically positive, FET-PET/MRI^{CR} was still considered valuable for ruling out other localizations, confirming that lesion 4 was resection cavity, and providing direction for surgery.

Case 7 (fig. 5): A 59-year-old female patient was diagnosed in 2020 with a GH secreting macroadenoma on the right side with cavernous sinus invasion (Knosp 3A, lateral extension). Preoperatively she received 2 SRL injections, after which she was operated (positive histology) without biochemical remission and was started on pegvisomant. Retrospectively, the remission chance of the previous surgery was estimated as unlikely because of the lateral cavernous sinus invasion. Postoperative MRI showed no definite residue (only postoperative changes in the right sella and right cavernous sinus). Because of persistent symptoms and increased IGF-1, FET-PET/MRI^{CR} was performed, showing increased tracer uptake lateral to the right carotid artery, confirming the impossibility of cure or improvement with revision TSS, and therefore preventing unnecessary surgery. She was treated with radiotherapy and is currently without medical treatment.

Case 8 (fig. 5): A 34-year-old female patient presented in another center in 2014 with acromegalic symptoms, including severe headache, and a 7 mm cystic intrasellar lesion on the left suspected for Rathke's cleft cyst (RCC; suboptimal baseline MRI-scan). Biochemical findings at initial presentation were inconclusive (normal GST, persistent mildly elevated IGF-1 (max SD +3.7)). A trial treatment with SRL was not effective (both biochemically and clinically) and was not tolerated well. Because of her acromegalic phenotype, persistent mildly elevated IGF-1 and persistent symptoms a TSS was performed in 2019 (negative histology). IGF-1 and symptoms did not improve postoperatively. She was started on pegvisomant and was referred to our center for a second opinion.

At the time of presentation at our center, she was clinically and biochemically not well controlled (IGF-1 +3.7 SD on high dose pegvisomant). Conventional MRI was suspected for an 8.7 mm lesion on the right side of the sella, possibly extending over the midline to the left, without cavernous sinus invasion (Knosp 1); a small remnant of the cystic lesion that was targeted during TSS in 2019 elsewhere suspected for a RCC was still visible. FET-PET/MRI^{CR} was performed to confirm these findings and indeed showed increased tracer uptake in the lesion on the right and no uptake in the cystic remnant lesion on the left. She was offered a revision TSS with the intention of biochemical remission and symptom relief, which was considered as possible, with an increased risk for CSF leakage (occurred in the first TSS) and pituitary insufficiency (revision TSS, small pituitary volume). Perioperative findings were positive, with confirmative histopathology. During postoperative course she was readmitted because of hyponatremia due to SIADH. Postoperative biochemistry improved but did not normalize, and her symptoms (mainly a severe headache) were not reduced (IOQ-3). Postoperative MRI showed no clear remnant lesion. At 3 months postoperative she was restarted on pegvisomant in combination with a low carbohydrate diet, under which IGF-1 has normalized (with a lower dose of pegvisomant than preoperatively) and she is symptom free.

In this patient with difficult biochemistry (increased IGF-1, normal GST) and a high need for alternative treatment because of severe headache, intolerance for SRL and little effect of pegvisomant on IGF-1 (only on high dose normalization and improvement of symptoms), with a difficult MRI (cystic lesion (in retrospect considered to be an RCC), and at reassessment here suspicion for a lesion on the right), FET-PET/MRI^{CR} was of added value to confirm the suspected lesion on the right side and diagnosis and to evaluate treatment options.

Case 10 (fig. 5): A 60-year-old female with a history of hypopituitarism was suspected of acromegaly because of suggestive symptoms, an increasing IGF-1, but paradoxical GST and inconclusive MRI. She

was treated with SRL and pegvisomant to gain more certainty, with improved biochemistry and clinical control but also side effects. FET-PET/MRI^{CR} was performed to gain more certainty and showed a mild asymmetry to the right. She underwent surgery with the primary goal to obtain tissue to confirm acromegaly (estimated as possibly), and as secondary goals (estimated as unlikely) to normalize IGF-1 and improve quality of life. Surgical findings and histology were positive, confirming the diagnosis of acromegaly. She experienced clinical improvement, and her biochemistry improved without need for medication (IOQ-1).

In this patient with inconclusive biochemistry and MRI and side effects on both SRL and pegvisomant, FET-PET/MRI^{CR} helped in obtaining more certainty about the diagnosis and in optimizing surgical outcome.