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Pancreatic Insulinoma: Experience of the Endocrinology Department at Mohammed VI University Hospital, Marrakesh, Morocco

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Abstract **Original Research Article**

Insulinoma is a rare pancreatic neuroendocrine tumour, usually benign and responsible for organic hypoglycaemia. This retrospective study, conducted at the endocrinology department of Mohammed VI University Hospital between 2017 and 2025, reports 13 cases of insulinoma. The average age at diagnosis was 46 years, with a predominance of females. The clinical manifestations were dominated by sweating (69%) and loss of consciousness (61%), with an average diagnostic delay of 28 months. Laboratory tests confirmed hyperinsulinemic hypoglycaemia, and pancreatic MRI allowed tumour localisation in 90% of cases. The majority of lesions were single, small (median 15 mm) and located in the tail of the pancreas. Surgical enucleation was the most commonly performed procedure (91%), with generally uncomplicated postoperative outcomes. Histological analysis confirmed well-differentiated neuroendocrine tumours, classified as G1 or G2 according to the Ki-67 index. The diagnosis of insulinoma is based on the combination of documented hypoglycaemia and high-performance imaging, particularly MRI. Conservative surgery remains the standard treatment. Genetic testing should be considered if MEN1 is suspected

Keywords: Pancreatic Insulinoma, Pancreatic Neuroendocrine Tumour, Organic Hypoglycaemia, Fasting Test, Endoscopic Ultrasound, Pancreatic Surgery, Immunohistochemistry, Follow-Up.

INTRODUCTION

Insulinomas are the most common functional neuroendocrine tumours of the pancreas, arising from the β cells of the islets of Langerhans. They account for approximately 1 to 2% of pancreatic tumours. They occur at any age and are mostly benign, solitary and small (< 2 cm) [1]. In 5 to 10% of cases, they are part of type 1 multiple endocrine neoplasia syndrome. Diagnosis is based on evidence of endogenous hyperinsulinism during prolonged fasting tests, while advances in imaging have improved preoperative localisation [2, 3]. Treatment is mainly surgical, with a generally favourable prognosis, however malignant forms remain rare.

The aim of this study is to evaluate the clinical characteristics, diagnostic methods, essential elements of surgical management and evolutionary profile of patients with pancreatic insulinoma.

METHODS

We conducted a retrospective, descriptive, single-centre study including patients treated for pancreatic insulinoma between January 2017 and January 2025 in the endocrinology department of Mohammed VI University Hospital in Marrakesh.

All patients meeting the diagnostic criteria for pancreatic insulinoma established by the Endocrine Society, based on clinical, biological, radiological and histopathological findings, were included. All patients with other causes of hypoglycaemia, as well as those with incomplete medical records, were excluded from the study.

Data were collected from medical records and the 'HOSIX' computerised archiving platform, including epidemiological variables (incidence, age at diagnosis, sex), clinical variables (time between onset of symptoms and diagnosis, adrenergic signs, neuroglycopenic signs,

etc.), biological variables (fasting test, blood glucose at the time of symptoms, indulinemia, C-peptide, etc.), radiological (abdominal-pelvic CT scan, pancreatic MRI, echoendoscopy, etc.), therapeutic (medical treatment, surgical treatment, etc.), histopathological, and evolutionary (remission, recurrence, death, etc.) variables.

Statistical analysis was performed using Microsoft Excel 2016 software. Quantitative variables were presented as mean ± standard deviation, while qualitative variables were expressed as percentages.

RESULTS

We included 13 cases of pancreatic insulinoma in our study, representing an estimated incidence of 1.8 cases/year. The sex ratio was 1.60 in favour of a female predominance, with a mean age at diagnosis of 46 years +/- 12.5 years.

All patients in our serie presented adrenergic manifestations of hypoglycaemia and 92% reported neuroglycopenic signs. The most common symptoms were sweating (69%), followed by loss of consciousness (61%). No clinical signs suggestive of NEM1 syndrome were identified. The average time to diagnosis, which was prolonged to 28.6 months, reflects the non-specific and misleading nature of the symptoms.

Biologically, all patients had significant hypoglycaemia during the fasting test. The average blood glucose level measured at the time of symptoms was 0.34 ± 0.094 g/L, confirming endogenous hyperinsulinism. The average insulin level was 33.62 µIU/mL, associated with an average C-peptide level of 4.29 ng/mL. Furthermore, screening for multiple endocrine neoplasia type 1 (MEN1), including the recommended hormone and biological tests, was negative in all patients.

Pancreatic MRI was the main morphological examination used for localisation in our series, performed in 11 patients due to its sensitivity and availability in our setting (Figure:1). It enabled the location of the tumour to be identified in 90% of cases. Abdominal computed tomography was performed in 7 patients, while octreoscan (octreotide scintigraphy) (Figure: 2) and upper echoendoscopy were performed in 2 and 4 patients, respectively. The median size of insulinomas was 15.16 mm, with a predominance of localisation in the tail of the pancreas (41%), followed by the isthmus (25%), the head (25%) and the pancreatic body (14%). No localisation was detected in a single patient. Intraoperative exploration identified the tumour in all patients.

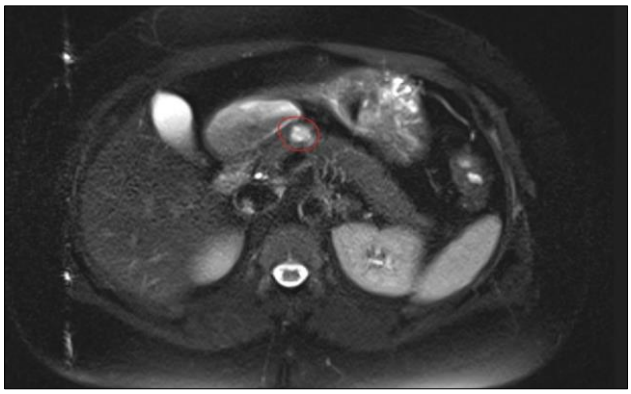

Figure 1: Axial MRI of the pancreas revealing a T2-hyperintense lesion measuring 2 cm x 2 cm in the isthmus of the pancreas

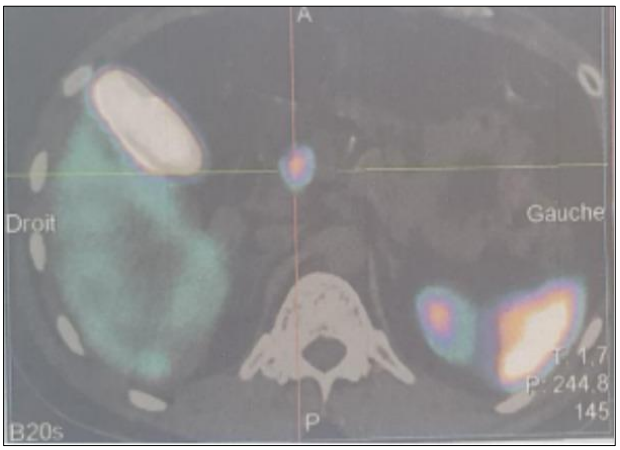

Figure 2: Octreoscan revealing a fixation focus at the head-neck junction of the pancreas

In terms of treatment, all patients benefited from lifestyle and dietary measures, combined with medication appropriate to the severity of their hypoglycaemia (diazoxide, calcium channel blockers or corticosteroids). This management allowed effective control of hypoglycaemic episodes preoperatively, facilitating preparation for surgery, which was generally performed quickly after diagnostic confirmation. The only patient who did not undergo surgery was treated with diazoxide, with satisfactory clinical improvement and generally good tolerance. In the 12 patients who underwent surgery, the approach used was laparotomy. The surgical procedure mainly consisted of tumour enucleation (91% of cases), while caudal pancreatectomy was performed in 8.3% of cases, with satisfactory postoperative outcomes in all patients.

Anatomopathological examination, with immunohistochemistry, confirmed the neuroendocrine nature of all tumours. The mitotic index was less than 2% in 41% of cases. According to the WHO classification, lesons were classified as NET G1 in 41% of cases and NET G2 in 58%. The Ki-67 proliferation index, with an average value of 4.7%, reflected overall low to moderate proliferative activity. Diffuse and constant expression of chromogranin A and synaptophysin was observed in all samples, confirming the well-differentiated nature of tumours.

The outcome after treatment was favourable for all patients. All patients who underwent surgery achieved complete clinical and biological remission, with no recurrence during follow-up. The patient treated medically achieved sustained control of hypoglycaemia with diazoxide. No deaths were reported.

DISCUSSION

We included 13 cases of pancreatic insulinoma in our study, representing an estimated incidence of 1.8 cases/year. The sex ratio was 1.60 in favour of a female predominance, with a mean age at diagnosis of 46 years +/- 12.5 years, in accordance with the findings of Hacışahinoğulları *et al*., (43.9 ± 12.5 years) [4], with a mild female predominance (F/M = 1.16), as reported by Furnica *et al*., (1.66) [5].

The main diagnostic feature of insulinoma is Whipple's triad, first described in 1938 by Allen Whipple. It combines clinical manifestations suggestive of hypoglycaemia, including neurovegetative and/or neuroglycopenic signs, biologically documented hypoglycaemia at the time of symptoms, and the disappearance of these symptoms after glycaemic correction. This triad remains the clinical basis for the diagnosis of pathological hypoglycaemia, particularly that associated with endogenous hyperinsulinism.

All patients developed adrenergic manifestations, while 92% reported signs of neuroglycopenia. The most frequently observed symptoms were sweating (69%), followed by loss of consciousness (61%), results similar to those reported by Li *et al*., [6]. No clinical signs suggestive of multiple endocrine neoplasia type 1 (MEN1) were identified. The average time to diagnosis, reaching 28.6 months, reflects the non-specific and sometimes misleading nature of the clinical presentation, with this delay often attributed to other psychiatric, neurological or metabolic conditions. This result is consistent with several studies, notably those by Li *et al*., (20.4 ± 15.7 months) [6], and Hacışahinoğulları *et al*., (36 months) [4].

The biological criteria used to document insulin hypersecretion in our series are in line with the recommendations of European (ENETS: European Neuroendocrine Tumor Society) and American (Endocrine Society) expert societies [7, 6]. They are based on a fasting test with concomitant measurement of insulin, C-peptide and proinsulin levels, in the context of significant hypoglycaemia, enabling the establishment of a biochemical profile characteristic of endogenous hyperinsulinism.

The median venous blood glucose level observed was 0.35 g/L, confirming significant hypoglycemia at the time of symptoms. This value is comparable to those reported by Yumuk *et al*. (0.39 ± 0.13 g/L) and Hacışahinoğulları *et al*., (0.39 g/L) [5,8], and falls within the diagnostic thresholds recommended by ENETS (< 0.45 g/L) and the Endocrine Society (< 55 mg/dL) [9].

The median insulin level in our cohort was 24.3 µU/mL, which falls within the ranges reported in the literature, notably by Hacışahinoğulları *et al*., (16 µU/mL), Yumuk *et al*., (32.15 ± 32.53 µU/mL) and Li *et al*., (40.32 ± 21.75 µU/mL) [8, 4]. Similarly, C-peptide was elevated (3.8 ng/mL), concordant with the data from Yumuk *et al*., and Li *et al*., [8, 4], with variations attributable to inter-individual heterogeneity and the stage of fasting at the time of sampling. Overall, these results are consistent with those reported in the literature and confirm the diagnostic value of the triad of hypoglycaemia, hyperinsulinaemia and elevated C-peptide levels in the positive diagnosis of insulinoma.

Regarding the screening for multiple endocrine neoplasia type 1 (MEN1), some series report a significant association. In the study by Wei Li *et al*., [6], MEN1 was identified in 3 patients (3.9%). Similarly, Hacışahinoğulları *et al*., [4], describe, among 12 cases of insulinoma, a patient with primary hyperparathyroidism associated with Cushing's disease, suggesting a condition compatible with MEN. In our study, none of the patients presented clinical, biological or morphological evidence suggestive of MEN1, which is consistent with data reported in several cohorts where insulinoma remains sporadic in the majority of cases.

The morphological localisation examinations used in our serie showed a clear superiority of pancreatic MRI, with a sensitivity of 90%, followed by abdominal CT scan (71%), then echoendoscopy and octreotide scintigraphy (50% for each). The sensitivity obtained with CT is comparable to that reported by Li *et al*., [6], but remains higher than the rates reported by Peltola and Andreassen [10, 11], these variations are probably related to the heterogeneity of imaging protocols and tumour size.

Pancreatic MRI enabled the localisation of insulinomas in approximately 90% of cases, with a higher performance than that reported by Li *et al*., (78.8%), Peltola (50%) and Andreassen (58%) [6-11]. This performance is more specific for millimetre-sized insulinomas, which are frequently located in the tail of the pancreas, representing the predominant location in our study. The low sensitivity observed for echoendoscopy in our cohort (50%) is mainly explained by the limited number of examinations performed, due to limited accessibility in our context, as well as the influence of tumour location. Octreotide scintigraphy remains less effective due to the low expression of somatostatin receptors in insulinomas.

Published data confirm that insulinomas are usually small in size. Li *et al*., report an average size of 1.62 ± 0.59 cm, while Hacışahinoğulları *et al*., describe an average of 16.7 mm, values very close to those observed in our series (15.16 mm) [4-6]. In our study, the tail of the pancreas was the most common location for insulinomas (41.66%), the same trend found in the series by Yumuk *et al*., estimated at 42.9% [8].

The management of hypoglycaemia associated with insulinoma is initially based on dietary measures, including a split diet rich in complex carbohydrates to avoid prolonged periods of fasting. In cases of acute hypoglycaemia, the administration of simple carbohydrates or IV glucose is essential. Pharmacologically, diazoxide is the first-line treatment in advanced or inoperable cases. In cases of refractory hypoglycaemia, the adjunctive use of glucocorticoids, calcium channel blockers (verapamil) or phenytoin (diphenylhydantoin) has been described.

In localised forms, surgery remains the standard treatment, predominantly enucleation. In our study, 91% of patients underwent enucleation, while only one case (8.3%) required caudal pancreatectomy. These results are consistent with those reported by Li *et al*., where enucleation accounted for 65.79% of procedures, ahead of distal pancreatectomies (19.74%) and more complex cephalic resections (7.89%) [6]. However, in advanced or metastatic forms, other therapeutic approaches may be considered. These include somatostatin analogues (SSAs), internal radiation therapy (PRRT), certain chemotherapies, and local-regional treatments such as radioembolisation or chemoembolisation, which are particularly indicated in aggressive insulinomas.

Insulinomas are well-differentiated pancreatic neuroendocrine tumours whose trabecular, acinar or solid architecture makes them indistinguishable from other pancreatic NETs. Their classification is based on the 2019 WHO criteria [12], primarily proliferative activity assessed by the number of mitoses and the Ki-67 index, which are essential for prognostic stratification. Immunohistochemically, insulinomas typically express chromogranin A and synaptophysin, confirming their neuroendocrine nature. Loss of p57 expression and the occasional presence of amyloid deposits of amylin are factors contributing to the diagnosis. Aggressive forms have a distinct profile, characterised by expression of ARX and alpha-1-antitrypsin, decreased expression of insulin, PDX1 and GLP-1R, and molecular alterations such as ATRX/DAXX mutations or chromosomal instability. In our series, the histoprognostic study revealed well-differentiated NETs, with a median KI 67 of 3% and a grade of 2 in the majority of cases, which is consistent with the results of the study by Andreassen *et al*., Furthermore, chromogranin A and synaptophysin were positive in 100% of cases, as reported by Li *et al*., [6-12].

After resection of a benign insulinoma, prolonged follow-up is recommended, based on targeted clinical assessment, biological tests (blood glucose, insulin, C-peptide, proinsulin) and morphological imaging, mainly MRI. Closer monitoring is indicated in patients with MEN1 due to the increased risk of recurrence. In cases of malignant insulinoma, follow-up is more intensive and tailored to tumour aggressiveness and symptom control, in accordance with ESMO recommendations [13], combining regular clinical, biological and radiological monitoring.

The majority of insulinomas (90–95%) are benign and associated with an excellent prognosis, with a 5-year survival rate of 95–100% after surgery and a low recurrence rate. Conversely, malignant forms have a more guarded prognosis, with a median survival of approximately 2 years. Nevertheless, their management remains justified, given the improvement in symptom control and quality of life. In our series, complete clinical remission was achieved in 92.3% of patients, a result consistent with the data reported in the literature. The only patient who did not undergo surgery is currently undergoing additional investigations to determine the location of the tumour in order to ensure appropriate therapeutic management. [13].

CONCLUSION

Pancreatic insulinoma, although rare, is a potentially curable cause of organic hypoglycaemia. In our study, early clinical recognition of symptoms enabled rapid diagnosis, limiting the delays usually

reported. Management was based on effective multidisciplinary collaboration, leading to surgery within an optimal timeframe and complete remission in the majority of patients who underwent surgery. Several limitations should be acknowledged, including limited availability of specific biochemical assays, restricted access to advanced functional imaging, and the underuse of endoscopic ultrasonography. In addition, the absence of MEN1 genetic testing and the short follow-up period represent important constraints. Nevertheless, our findings underscore the value of thorough clinical assessment and coordinated multidisciplinary management. Enhancing diagnostic resources and reinforcing long-term follow-up are essential to further optimize insulinoma care in line with international standards.

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