CASE REPORT

Endoscopic Ultrasound-Guided Radiofrequency Ablation as Therapeutic Approach for Pancreatic Insulinoma

DARSHINI S[1], KHAIRUL NAJMI MN[1], KOK WH[1], LEE CC[1], WOO WH[1], WONG Z[2]

[1]Gastroenterology and Hepatology Unit, Department of Medicine, Faculty of Medicine, Universiti Kebangsaan Malaysia, Jalan Yaacob Latif, 56000 Cheras, Kuala Lumpur Malaysia
[2]Pantai Hospital Kuala Lumpur, Bangsar, Kuala Lumpur

Received: 29 June 2023 / Accepted: 14 August 2023

ABSTRAK

Insulinoma merupakan salah satu jenis tumor neuroendokrin fungsi pankreas (PNET) yang paling lazim dan sering ditunjukkan dengan hipoglisemia simptomatik yang memburukkan keadaan pesakit. Apabila imej konvensional gagal untuk mengesan lesi, ultrabunyi endoskopik (EUS) telah terbukti berguna dalam menentukan penempatan praoperasi serta dengan pengambilan sampel biokimia melalui aspirasi jarum halus terhadap lesi yang disyaki. Reseksi pembedahan telah menjadi rawatan piawai bagi tumor neuroendokrin pankreas ini. Walau bagaimanapun, dengan kemajuan terkini, ablasi radiofrekuensi panduan ultrabunyi endoskopik (EUS-RFA) telah muncul sebagai pendekatan terapeutik yang menjanjikan dan kurang invasif dengan hasil yang baik dan komplikasi yang rendah. Kami melaporkan seorang pesakit dengan insulinoma pankreas bersimptomatik yang dirawat dengan EUS-RFA.

Kata kunci: Ablasi radiofrekuensi; insulinoma pankreas; ultrabunyi endoskopik

ABSTRACT

Insulinoma is one of the most prevalent form of functional neuroendocrine tumor of the pancreas (PNET) that often manifests with debilitating symptomatic hypoglycemia. When conventional imaging fails to detect the lesion, endoscopic ultrasound (EUS) have proven to be of value to determine the preoperative

Address for correspondence and reprint requests: Khairul Najmi Muhammad Nawawi. Gastroenterology and Hepatology Unit, Department of Medicine, Faculty of Medicine, Universiti Kebangsaan Malaysia, Jalan Yaacob Latif, 56000 Cheras, Kuala Lumpur Malaysia. Tel: +6018-3734807 Email: khairulnajmi84@gmail.com

localisation as well as with biochemical sampling via fine needle aspiration of the suspected lesion. Surgical resection has been the standard care for these pancreatic neuroendocrine tumors. However, with recent advancements, endoscopic ultrasound-guided radiofrequency ablation (EUS-RFA) has emerged as a promising and less invasive therapeutic approach that carries a favourable outcome and a low risk of complications. We report eda patient with symptomatic pancreatic insulinoma who was treated with EUS-RFA.

Keywords: *Endoscopic unltrasound; pancreatic insulinoma; radiofrequency ablation*

INTRODUCTION

Pancreatic insulinoma is a functional neuroendocrine tumour (NET) that is related to endogenous hypersecretion of insulin occurring in 1 to 4 people per million of the general population (Okabayashi et al. 2013). Typically, pancreatic insulinoma manifests as a solitary benign tumour. However, it can also be linked to multiple endocrine neoplasia type 1 (MEN1). In normal circumstances, elevated plasma glucose levels would stimulate the release of insulin. However, in the case of an insulinoma, insulin is still secreted despite low levels of plasma glucose (Zhuo & Anastasopoulou 2022). Fasting hypoglycemia is the most characteristic finding alongside postprandial hypoglycemia (Placzkowski et al. 2009). Typical autonomic symptoms observed in insulinoma consist of diaphoresis, palpitations, and tremulousness, while neuroglycopenic symptoms involve cognitive dysfunction, confusion, bizarre behaviour, slurred speech, blurred vision, seizure, and coma.

Insulinoma should be considered in individuals with Whipple's triad, which is characterised by symptomatic hypoglycaemia, low plasma glucose concentration, and improvement in glucose replacement. Evaluation via biochemical testing and localisation of tumour is of utmost importance to evaluate an insulinoma. The 72-hour fasting test, along with the assessment of plasma insulin, C-peptide and proinsulin levels during episodes of hypoglycaemia, serves as the gold standard for biochemical testing with the capability to detect nearly 99% of insulinomas (Salazar et al. 2012). Contrast-enhanced computed tomography (CT) is commonly employed as a non-invasive imaging technique, with a success rate of 70 to 80% for effective preoperative localisation but CT is insensitive to detecting pancreatic lesions that are less than 2 cm (Eloubeidi et al. 2016). When CT findings fail to detect lesions in those with high suspicion for insulinoma, endoscopic ultrasonography (EUS) should be the next alternative as it has a sensitivity of up to 95% in localisation of the tumour. It is also helpful not only in localisation but also with tissue acquisition can be done in the same setting (Khashab et

al. 2011).

While medications may help with short-term symptom control, surgical resection or enucleation has been known to be the standard care for these pancreatic NET. However, with recent advancements, endoscopic ultrasonography-guided radiofrequency ablation (EUS-RFA) has been increasingly popular as a minimally invasive and locally ablative procedure with the promising outcome (Svoboda et al. 2021). This procedure can be done in one hour and has minimal complications following the interventions. The aim of this procedure is to achieve euglycemia.

CASE PRESENTATION

A 53-year-old woman who underwent distal pancreatectomy and splenectomy in 1997 for mucinous cystadenoma presented with recurrent hypoglycemic symptoms for 2 months. These symptoms usually occur 4 to 5 hours postprandial which then resolved with food intake. Her lowest blood glucose reading was documented at 2.4 mmol/L. On further testing during her fasting hypoglycemia, she exhibited an elevated C-peptide at 1570 pmol/l and insulin levels at 50.26 IU/ml along with normal insulin-like growth factor 1 (IGF-1) and cortisol levels. The initial CT liver multiphase failed to detect any pancreatic lesion, hence she was referred for an EUS. EUS demonstrated a pancreatic lesion measuring 1 x 0.3 x 0.86 cm arising from the body of pancreas (Figure 1). We then proceeded onto doing an endoscopic fine needle aspiration in the same setting, which was consistent with a pancreatic NET that stains for chromogranin and synaptophysin (Figure 2).

Subsequently, she underwent radiofrequency ablation (RFA) under EUS guidance. A linear ultrasound endoscope with a frequency of 7.5 MHz was utilised to locate the mass. Then, an EUS-RFA needle was inserted through the endoscope and positioned

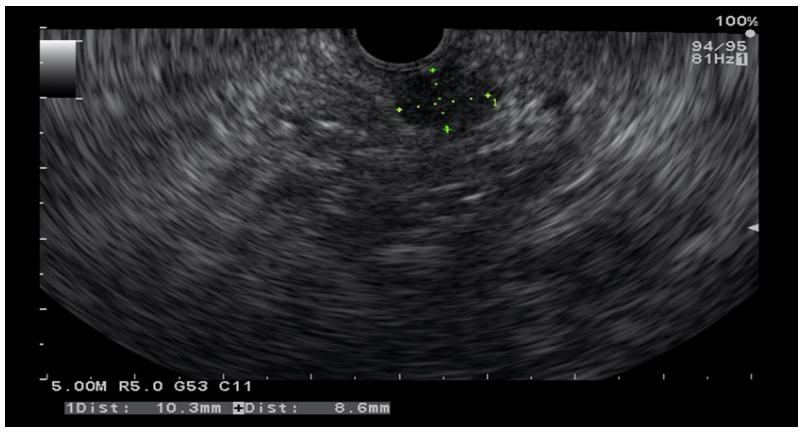

FIGURE 1: Hypoechoic circular pancreatic lesion at body of pancreas (10.3 x 8.6mm) on endoscopic ultrasound (EUS)

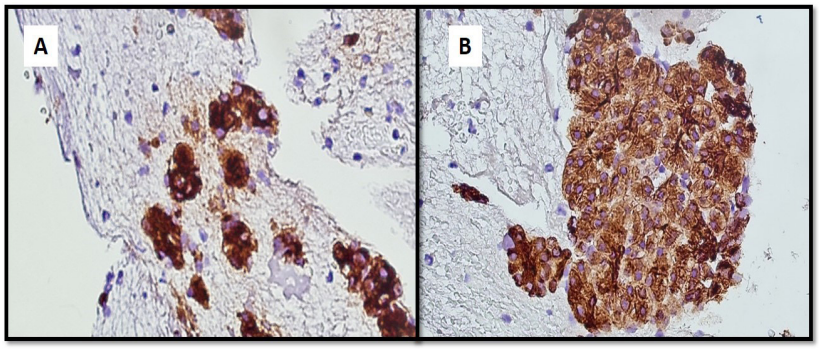

FIGURE 2: Immunohistochemical staining showing cells positive for synaptophysin (A) and chromogranin A (B) consistent with neuroendocrine tumours.

within the lesion. The needle had a sharp tip and a diameter of 19G with a distal ablation area measuring 10 mm. A total of three ablations of were administered, each lasting 10 seconds and using a power of 30W until an echogenic bubble effect was visualised (Figure 3a & b). The catheter used for ablation was taken out and carefully inspected. There was no immediate complication was observed. Following the procedure, her blood glucose normalised and she was able to be weaned off diazoxide which was used to treat her hypoglycemia prior to the procedure. She was then discharged two days post-procedure. A surveillance CT post RFA done 6 weeks later showed a reduction in tumor size (1.4 x 1.4 cm) in comparison to the previous CT scan (1.4x 1.6 cm).

Three months later she developed recurrent episodes of hypoglycemia for a period of 1 week for which she was then restarted on diazoxide. Repeated CT showed a pancreatic lesion measuring 0.7 x 0.9 cm. She subsequently underwent a second RFA. A total of 3 ablations were performed with 30 W for 10 seconds each. Post procedure noted reduced vascularity in the lesion (Figure 3c), and she was weaned off diazoxide as she became asymptomatic post-ablation. A repeated surveillance scan 6 weeks later noted a residual enhancing lesion. She had since remained asymptomatic at 6-month follow-up without signs of recurrent hypoglycaemia.

DISCUSSION

Insulinomas are usually occur in the head and body of the pancreas, and the majority of them are non-malignant. Surgical removal has traditionally been the primary approach for treating these symptomatic benign pancreatic lesions which may possibly lead to complications such as brittle diabetes and a negative sequalae of pancreatic insufficiency. However, in recent years, EUS-RFA has been proving to be a more attractive option in terms of safety and efficacy in both benign and malignant conditions. The first utilisation of EUS-guided RFA was demonstrated in a porcine model by Goldberg et al. in 1999. It is a good option in those who are frail and

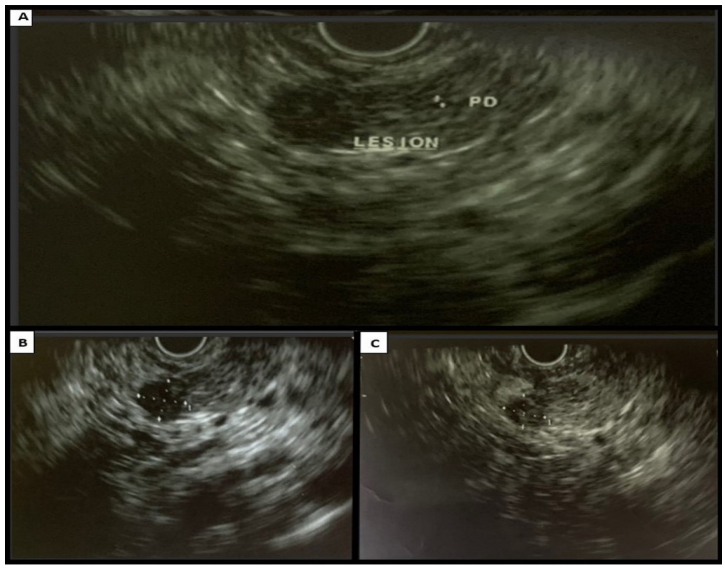

FIGURE 3: Endoscopic ultrasound-guided radiofrequency ablation (EUS-RFA); (a) A lesion located in the body of pancreas; (b) Endoscopic ultrasound guided RFA with echogenic bubbling; (c) Procedural outcome

elderly. As well as in those who are not keen for a surgical resection or wish for tissue sparing in those with a history of distal pancreatectomy in the past just as in our patient.

Limmer et al. (2009) was the first to report successfully treating insulinoma with CT-guided percutaneous RFA. Nevertheless, the pancreas is situated deep within the retroperitoneal space, making the application of CT-guided RFA in this manner potentially causes unintended punctures and thermal injury to neighbouring organs. EUS provides convenient access to the pancreas, making EUS-RFA a viable option for administrating ablative treatment to the lesions in the pancreas (El Sayed et al. 2021). EUS which was initially used as diagnostic modality with high accuracy as it is not limited by gastrointestinal gas and abdominal fat. EUS has since then rapidly found its role for a variety of therapeutic approach. In 2019, Barthet et al. (2019) conducted a prospective multicenter study which revealed the implementation of EUS-RFA technique had an efficacy rate of 86%. This study showed a complete resolution of 12 out of 14 lesions at 1 year post procedure.

EUS-RFA employs high-frequency alternating current to eliminate solid tumors by causing cellular damage through coagulation necrosis. The radiofrequency is emitted from a visible section of the electrode, generating ion movement within the nearby tissue. This ion movement results in heat generation due to friction, ultimately leading to the destruction of the targeted tissue (Gaidhane et al. 2012).

EUS-RFA is performed when a well sedated patient is put in the left lateral position. A linear array-

echoendoscope is employed and a 19G electrode needle which is connected to a radiofrequency generator is inserted into a target lesion to which a radiofrequency power of 30W is delivered. To minimise injury to the surrounding structures, the electrode used undergoes cooling using a chilled saline solution. The parameters including radiofrequency power, ablation duration, and the number of electrode passes required for successful ablation will be documented and recorded (Lakhtakia et al. 2016).

Post-procedure patient is observed for 24-48 hours for complications. The commonest side effect is related to the thermal injury to the pancreas causing acute pancreatitis followed by abdominal pain, gastrointestinal haemorrhages, pancreatic fistula, pseudocyst, and pancreatic or bile leak (Jonica & Wagh 2020). The response to the ablation is reflected by the resolution of symptoms such as hypoglycaemia with biochemical improvement. Lesion size should be reassessed with CT imaging in 6 months and repeated intervals. It is important to note that this technique should not be used in patients with cardiac pacemakers or other active implants (Chaudhary & Sun 2017).

In our patient EUS-RFA has proven to be successful as the patient is free of symptoms with no complications.

CONCLUSION

We believe that RFA under EUS guidance in the treatment of pancreatic insulinoma is an emerging modality of treatment. EUS-RFA has become a more widely used approach to treat a myriad of pancreatic lesion as it is a promising non-invasive technique that induces tissue necrosis of the localised lesion and would likely soon be a promising alternative to surgery.

ACKNOWLEDGEMENT

The author would like to acknowledge Gastroenterology Unit, Department of Medicine, Department of Radiology, Universiti Kebangsaan Malaysia.

REFERENCES

Barthet, M., Giovannini, M., Lesavre, N., Boustiere, C., Napoleon, B., Koch, S., Gasmi, M., Vanbiervliet, G., Gonzalez, J.M. 2019. Endoscopic ultrasound-guided radiofrequency ablation for pancreatic neuroendocrine tumors and pancreatic cystic neoplasms: A prospective multicenter study. *Endoscopy* **51**(9): 836-42.

Chaudhary, S., Sun, S.Y. 2017. Endoscopic ultrasound-guided radiofrequency ablation in gastroenterology: New horizons in search. *World J Gastroenterol* **23**(27): 4892-6.

Eloubeidi, M.A., Decker, G.A., Chandrasekhara, V., Chathadi, K.V., Early, D.S., Evans, J.A., Fanelli, R.D., Fisher, D.A., Foley, K., Hwang, J.H., Jue, T.L., Lightdale, J.R., Pasha, S.F., Saltzman, J.R., Sharaf, R., Shergill, A.K., Cash, B.D., DeWitt, J.M. 2016. The role of endoscopy in the evaluation and management of patients with solid pancreatic neoplasia. *Gastrointest Endosc* **83**(1): 17-28.

El Sayed, G., Frim, L., Franklin, J., McCrudden, R., Gordon, C., Al-Shamma, S., Kiss, S., Hegyi, P., Er ss, B., Hegyi, P.J. 2021. Endoscopic ultrasound-guided ethanol and radiofrequency ablation of pancreatic insulinomas: A systematic literature review. *Therap Adv Gastroenterol* **14:** 17562848211042171.

Gaidhane, M., Smith, I., Ellen, K., Gatesman, J., Habib, N., Foley, P., Moskaluk, C., Kahaleh, M. 2012. Endoscopic ultrasound-guided radiofrequency ablation (EUS-RFA) of the pancreas in a porcine model. *Gastroenterol Res Pract* **2012:** 431451

Goldberg, S.N., Mallery, S., Gazelle, G.S., Brugge, W.R. 1999. EUS-guided radiofrequency ablation in the pancreas: results in a porcine model. *Gastrointest Endosc* **50**(3): 392-401.

Jonica, E.R., Wagh, M.S. 2020. Endoscopic treatment of symptomatic insulinoma with a new EUS-guided radiofrequency ablation device. *VideoGIE* **5**(10): 483-5.

Khashab, M.A., Yong, E., Lennon, A.M., Shin, E.J., Amateau, S., Hruban, R.H., Olino, K., Giday, S., Fishman, E.K., Wolfgang, C.L., Edil, B.H., Makary, M., Canto, M. I. 2011. EUS is still superior to multidetector computerized tomography for detection of pancreatic neuroendocrine tumors. *Gastrointest Endosc* **73**(4): 691-6.

Lakhtakia, S., Ramchandani, M., Galasso, D., Gupta, R., Venugopal, S., Kalpala, R., Reddy, D.N. 2016. EUS-guided radiofrequency ablation for management of pancreatic insulinoma by using a novel needle electrode (with videos). *Gastrointest Endosc* **83**(1): 234-9.

Limmer, S., Huppert, P.E., Juette, V., Lenhart, A., Welte, M., Wietholtz, H. 2009. Radiofrequency ablation of solitary pancreatic insulinoma in a patient with episodes of severe hypoglycemia. *Eur J Gastroenterol Hepatol* **21**(9): 1097-101.

Okabayashi, T., Shima, Y., Sumiyoshi, T., Kozuki, A., Ito, S., Ogawa, Y., Kobayashi, M., Hanazaki, K. 2013. Diagnosis and management of insulinoma. *World J Gastroenterol* **19**(6): 829-37.

Placzkowski, K.A., Vella, A., Thompson, G.B., Grant, C.S., Reading, C.C., Charboneau, J.W., Andrews, J.C., Lloyd, R.V., Service, F.J. 2009. Secular trends in the presentation and management of functioning insulinoma at the Mayo Clinic, 1987-2007. *J Clin Endocrinol Metab* **94**(4): 1069-73.

Salazar, R., Wiedenmann, B., Rindi, G., Ruszniewski, P. 2012. ENETS 2011 consensus guidelines for the management of patients with digestive neuroendocrine tumors: An update. *Neuroendocrinol* **95**(2): 71-3.

Svoboda, C., Pachofszky, T., Mitrovits, N., Stimakovits, J., Schleischitz, A., Püspök, A. 2021. Endoscopic Ultrasound-guided radiofrequency ablation for treatment of benign insulinoma. *Endoscopy* **53**(S01): S234.

Zhuo, F., Anastasopoulou, C. 2022. Insulinoma. In *StatPearls [Internet]*. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK544299/ [8 March 2023]