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Publication Date

2015-09-01

DOI

10.1136/bcr-2015-211778

Peer reviewed

CASE REPORT

Indocyanine green fluorescence-guided redo parathyroidectomy

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Accepted 18 August 2015

SUMMARY

Re-operative neck surgery for hyperparathyroidism is a technically difficult operation that requires adjunctive studies to assist with finding the parathyroid tissues. Intraoperative tests help minimise exploration of the neck and decrease injuries to the surrounding structures. Indocyanine green is a near-infrared fluorescent dye that in pre-clinical models was found to be useful in locating the parathyroid glands of dogs. No study has yet reported its use as a tool for parathyroid localisation in humans. We investigated the use of indocyanine green to assist with localisation of a recurrent parathyroid adenoma using a near-infrared imaging system. After exposure of the neck tissues, the parathyroid gland fluoresced brightly and directed our dissection. Exploration of the neck was minimal, and allowed for fast localisation and excision of the adenoma. Overall, use of indocyanine green is a simple and safe technique of intraoperative parathyroid localisation that warrants further investigation.

BACKGROUND

Primary hyperparathyroidism affects 1 in 1000 people in the USA, and surgery is successful as a treatment in 95% of cases.¹ However, patients who undergo redo neck exploration have an increased rate of injury to the recurrent laryngeal nerve, permanent hypocalcaemia and decreased cure rates due to ectopic glands.² This operation is technically challenging, and it is difficult to find the parathyroid glands due to scar tissue, ablation of the surgical planes and distortion of anatomy. It requires adjunctive testing both preoperatively (localisation imaging studies—sestamibi scan, CT scan, MRI) and intraoperatively (nerve monitoring, intraoperative parathyroid hormone (PTH) levels, frozen section) to successfully locate and resect the parathyroid tissues without damaging surrounding organs. Technology to intraoperatively image and localise the parathyroid is crucial to performing a safe and durable operation.

Indocyanine green (ICG) is a near-infrared (NIR) fluorescent agent that has been used medically in retinal angiography since the 1970s.³ It is a non-toxic compound that is injected intravenously and travels throughout the vasculature bound to plasma proteins. Organs that are highly vascularised fluoresce green and can be visualised using a camera system in the NIR range (800 nm wavelength). The dye is then taken up by the liver and has a short half-life in the vasculature as it is excreted through the biliary system within 3–5 min. The fluorescent agent has recently been

investigated to perform perfusion angiography in colorectal patients to analyse the quality of anastomosis, and in cholangiography during laparoscopic cholecystectomy.^{4–6} No human study has yet reported ICG use in parathyroid localisation, however, pre-clinical studies have shown it to be effective in localising parathyroid tissues in dogs.⁷ In this case report, we investigate its use as an adjunctive test to assist in localisation of a parathyroid adenoma.

CASE PRESENTATION

We present a case of a 75-year-old woman with recurrent hyperparathyroidism who, 20 years earlier, had been initially treated with a two-gland parathyroidectomy for primary hyperparathyroidism. She had no recurrent symptoms until 2 years prior, when she began to develop hypercalcaemia, chronic fatigue, depression, fatigue and abdominal pain. Her calcium and PTH continued to rise until 3 months prior, when she was admitted for acute hypercalcaemia with weakness, lethargy and severe abdominal pain. Her calcium at that time was 14 mg/dL and PTH level 417 pg/mL, with no palpable neck mass and a sestamibi scan of the neck negative for a recurrent adenoma. She was treated medically for hypercalcaemia with hydration and diuretic infusions and her calcium levels returned to 13 mg/dL. A contrast-enhanced CT of the neck showed a 2.7×2×3.5 cm heterogeneous soft tissue mass abutting the inferior and posterior aspect of the left thyroid lobe (figure 1). The lesion appeared separate from the left thyroid lobe and was likely a primary parathyroid lesion, such as an adenoma, or, given its size, possibly a parathyroid adenocarcinoma. The patient was referred for redo parathyroidectomy.



Figure 1 A contrast-enhanced CT of the neck showed a 2.7×2×3.5 cm heterogeneous soft tissue mass abutting the inferior and posterior aspect of the left thyroid lobe, with central hypoattenuation (yellow arrow).



To cite: Chakedis JM, Maser C, Brumund KT, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2015-211778

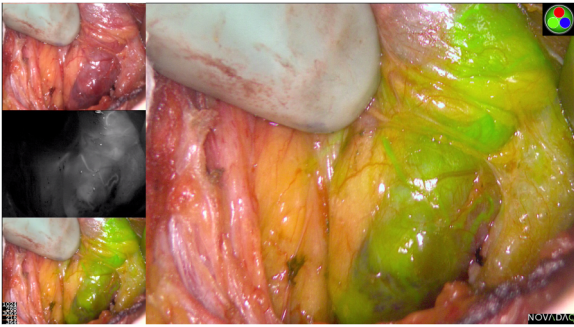


Figure 2 The left neck tissues are exposed and thyroid retracted. Twenty seconds after indocyanine green (ICG) injection the tissues on the left portion of the image were clearly demarcated with fluorescence. This directed our dissection to the area of the neck where the parathyroid adenoma was eventually found to be.

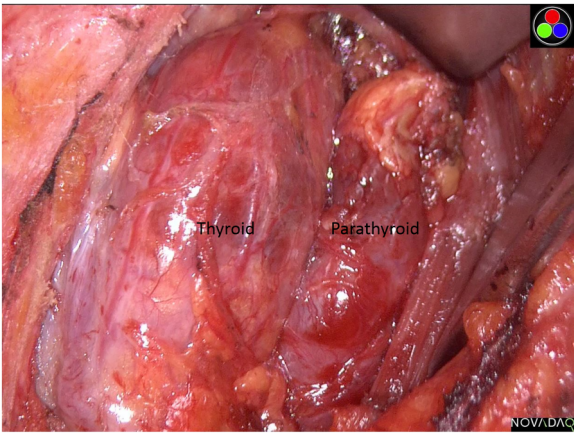
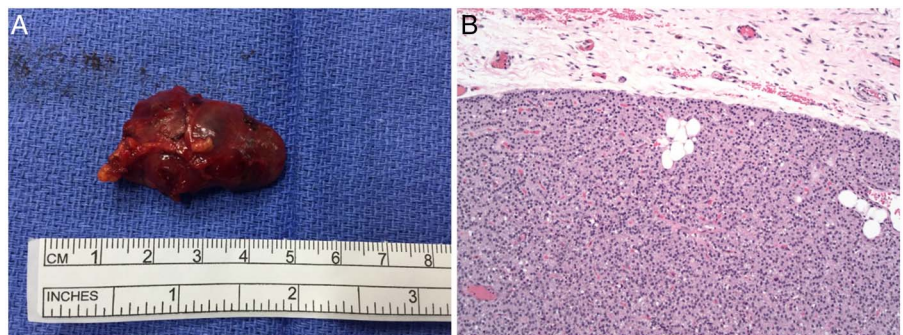


Figure 3 After dissection of the brightly fluorescent area, there was a mass that was a separate structure from the thyroid. It was soft with well-defined borders and consistent with a parathyroid adenoma.

INVESTIGATIONS

We investigated whether parathyroid tissue could be successfully located in a neck exploration using ICG. The patient consented to ICG injection in conjunction with her operation. Both the ICG compound and PINPOINT fluorescent imaging system (Novadaq) are Food and Drug Administration approved. (None of the listed authors have financial conflicts of interest with the Novadaq company.)

Figure 4 (A) Gross pathology after resection of the parathyroid adenoma. (B) Microscopic histopathology showing hypercellular parathyroid tissue consistent with an adenoma, at $\times 100$ magnification.



DIFFERENTIAL DIAGNOSIS

- ▶ Parathyroid Adenoma
- ▶ Parathyroid Carcinoma
- ▶ Multigland parathyroid hyperplasia

TREATMENT

Standard neck exploration was performed through the patient's prior transverse neck incision. We mobilised the strap muscles to expose the neck tissues. We then examined the left side of the neck, where scar tissue was encountered along with fullness of a mass in the left inferior parathyroid position. Before performing an extensive dissection of the area, we utilised the PINPOINT fluorescence imaging system to localise the parathyroid tissues. A 2.5 mg/mL bolus of 3 mL of ICG was used for intravenous injection and after 20 s there was a clear delineation of fluorescence from the left inferior portion of the neck (figure 2) followed by uptake in the thyroid. We then dissected this area of the neck to find the parathyroid gland (figure 3) and remove the gland. The recurrent laryngeal nerve was identified using nerve monitoring, and found to be intact. We utilised intraoperative PTH levels and found a drop from 523 pg/mL before excision down to 66 pg/mL 10 min later. Using intraoperative localisation in combination with intraoperative PTH levels, we were able to perform a minimal dissection on the left side of the neck to find and remove the parathyroid tissue. The operation took 1 h to perform, with 10 min devoted to using the fluorescent imaging system for localisation.

OUTCOME AND FOLLOW-UP

The next morning, the patient's calcium decreased to 11 mg/dL and PTH level decreased to 10 pg/mL. She had no complications from her operation and pathology showed a 5.9 g, 3.5 \times 1.7 \times 0.4 cm hypercellular parathyroid with nodular hyperplasia, consistent with a parathyroid adenoma (figure 4). One month after the operation, the patient's symptoms had improved, with increased energy and no abdominal problems. Her calcium was 9.8 mg/dL with a PTH level of 49 pg/mL.

DISCUSSION

ICG fluorescent imaging as an adjunct localisation study has not been previously reported in humans undergoing parathyroidectomy. In this case, we found that ICG localised the parathyroid adenoma from the surrounding thyroid and directed the dissection to a specific area. The limited amount of exploration we needed to perform simplified the operation. ICG and NIR imaging is simple and easy to use as it utilises the same basic laparoscopic instruments that surgeons are familiar with. The ICG compound is optimal for use in patients, as it is inexpensive and its safety profile is extremely high; however, it does contain

iodine and cannot be used in allergic patients. It works quickly to give fluorescence within seconds after injection and has a short half-life of minutes in the blood stream. A clinical limitation to this technique is that a specialised imaging system with both specific light source and camera filters is required.

Ultimately, we feel that ICG-guided parathyroidectomy can be clinically useful and deserves further investigation. There are

many questions as to the sensitivity and specificity for ICG localisation using this technique, especially in comparison to other experimental techniques such as methylene blue imaging. Currently, there is a clinical trial underway to investigate ICG-based assessment of parathyroid perfusion after total thyroidectomy (NCT02249780, clinicaltrials.gov). ICG-based technology has many advantages, making it attractive; however, more research is needed to understand how reliable it is for detection of specifically parathyroid adenomas and for identifying patients in whom it will make the most clinical impact.

Patient's perspective

The patient states that she feels physically and mentally better after her operation. "I have much more energy and am noticeably more alert. I haven't had any stomach pains since the operation."

Acknowledgements The authors would like to thank Dr Ahmed Shabaik for his assistance with the pathology images.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

Learning points

- ▶ Re-operative neck exploration is a technically difficult operation that requires multiple adjunctive studies to safely localise and excise the parathyroid tissue.
- ▶ Indocyanine green (ICG) can be utilised intraoperatively with a near-infrared (NIR) fluorescence imaging platform to successfully differentiate the parathyroid from thyroid and surrounding tissues.
- ▶ Further research is needed to determine how ICG and NIR imaging can be an effective adjunct to neck exploration for hyperparathyroidism.

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