

CONGENITAL HYPERINSULINISM FROZEN SECTION PROTOCOL

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PURPOSE:

- To help the surgeon with histologically corroborating the clinical impression of the diffuse or focal form of congenital hyperinsulinism
- In the focal form of congenital hyperinsulinism, to provide margin status

BACKGROUND:

Congenital hyperinsulinism is a group of rare genetic disorders characterized by dysregulated insulin secretion leading to hypoglycemia, frequently presenting at birth. Surgical intervention with partial or complete pancreatectomy may be required to prevent hypoglycemia and its severe consequences.

There are both diffuse and focal forms of congenital hyperinsulinism that require surgery; while they have similar prevalence, they require divergent surgical approaches and extents of pancreatectomy. These forms are characterized by different genetic, imaging and histologic findings, which should be used together by the Pathologist during intraoperative consultation.

PREPARATION PRIOR TO RECEIVING TISSUE SPECIMEN:

- Discuss with a Pediatric or GI Pathologist on the Congenital Hyperinsulinism Multidisciplinary Pathway Team to ensure backup may be available if desired
 - Drs. Jeffrey Goldstein, Bitu Naini, Hanlin Wang, Sarah Dry, David Dawson, Samuel French
- Review 18F-DOPA PET scan results:
 - Diffuse uptake suggests diffuse disease
 - Focal uptake suggests focal disease
 - Where within the pancreas is the lesion localized?
- Review genetic testing results:
 - Forms requiring surgery are caused by alterations either of two genes: *ABCC8* (encoding SUR1) and *KCNJ11* (encoding Kir6.2), both on chromosome 11p15, and both of which encode subunits of the Beta cell ATP-dependent potassium channel
 - Diffuse form is caused by homozygous loss of function mutations in either gene
 - Focal form is caused by a paternally-inherited heterozygous loss of function mutation in either gene, co-occurring with somatic loss of heterozygosity
 - A heterozygous result can be difficult to interpret without parental genetic comparison; furthermore, rare dominant mutations leading to diffuse disease have been described
 - Other genetic alterations leading to congenital hyperinsulinism (e.g. *GLUD1*, *GCK*, *HADHSC*) are medically treatable with diazoxide or octreotide; histologic evaluation of the pancreas is not usually helpful in guiding management of these patients
 - Rarely, Beckwith Wiedemann patients may come to surgery for control of hyperinsulinism; histologically, the pancreas shows diffuse endocrine proliferation throughout the pancreas occupying most of parenchyma, with scattered islet cell nucleomegaly

EXPECTED SPECIMENS:

- Initial frozen specimens typically consistent of pancreas biopsies to identify the lesion, which should be entirely submitted
- For focal lesions, subsequent frozen margin specimens may be expected

MACROSCOPIC AND MICROSCOPIC EXAMINATIONS:

- Diffuse
 - No gross changes
 - Normal microscopic tissue architecture
 - Islets are normal in size and distribution, and exhibit nucleomegaly, defined by nuclei 3x the size of surrounding nuclei
 - Within a single islet, only patchy nucleomegaly may be seen
- Focal
 - May show a red-pink lesion with poorly demarcated borders (though border may not be appreciable in a biopsy specimen)
 - Architecture-disrupting lesion shows adenomatous hyperplasia, a confluent endocrine cell proliferation in which about 40% of the cellularity within the lesion consistent of endocrine cells
 - Infiltrative borders may not be appreciable grossly, making frozen margins important

SIMPLIFIED SUMMARY:

	Imaging	Genetics	Histology	Surgery	Frozen goals
Diffuse	Diffuse uptake	Homozygous mutation	Diffuse islets showing nucleomegaly	Near total pancreatectomy	- Diagnostic corroboration
Focal	Focal uptake	Heterozygous mutation	Focal adenomatous lesion with endocrine cell hyperplasia	Partial pancreatectomy with margins	- Diagnostic corroboration - Margins

APERIO LINKS TO PRIOR UCLA CASES:

Accessible from UCLA campus only; if you receive an error message, it may help to log into Aperio before opening link.

[Congenital hyperinsulinism, diffuse](#)

[Congenital hyperinsulinism, focal \(Part A only\)](#)

FOR DIFFICULT CASES WITH UNCERTAINTY:

- Consult a Pediatric or GI Pathologist on the Congenital Hyperinsulinism Multidisciplinary Pathway Team
 - Drs. Jeffrey Goldstein, Bita Naini, Hanlin Wang, Sarah Dry, David Dawson, Samuel French
- If you don't appreciate either an adenomatous lesion or islet cell nucleomegaly, you may have an area of normal pancreas, while a focal lesion goes unsampled
- Deeper sections may help to show patchy nucleomegaly within an islet

PHOTOGRAPHIC EXAMPLES:

Lonlay-Debeney et al., Clinical Features of 52 Neonates with Hyperinsulinism. N Engl J Med 1999; 340:1169-1175. doi: 10.1056/NEJM199904153401505

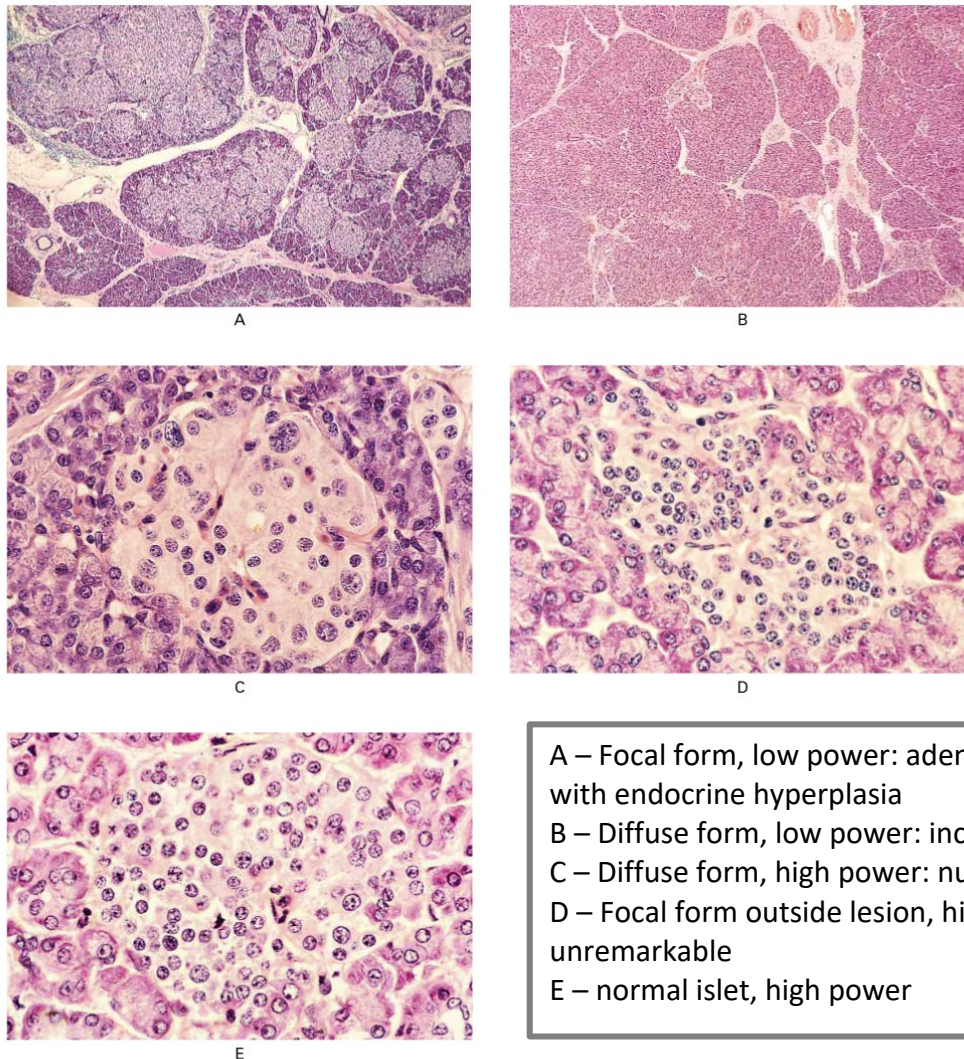


Figure 1. Microscopical Sections of the Pancreas from Neonates with Hyperinsulinemic Hypoglycemia. Panel A shows focal islet-cell abnormalities (focal hyperinsulinism) formed by the confluence of apparently normally organized islets (2.5 to 7.5 mm in diameter); the exocrine tissue is restricted to the periphery of the pancreatic lobule (hematoxylin and eosin, $\times 25$). Panel B shows a specimen from a neonate with diffuse hyperinsulinism; there is no obvious abnormality at this low magnification (hematoxylin and eosin, $\times 25$). At a higher magnification (Panel C), diffuse hyperinsulinism is characterized by large beta cells with abundant cytoplasm and abnormally large nuclei (up to 19 μm in diameter) within otherwise normal islets (hematoxylin and eosin, $\times 315$). Panel D shows focal hyperinsulinism outside the focal lesion. The nonfunctioning islet has small and normal beta-cell nuclei (hematoxylin and eosin, $\times 315$). Panel E shows an islet from an infant with normal glycemic control. The nuclei of normal beta cells and exocrine cells are an average of 5 to 6 μm in diameter (hematoxylin and eosin, $\times 315$).

A – Diffuse form, nucleomegaly
B – Focal form, adenomatous lesion

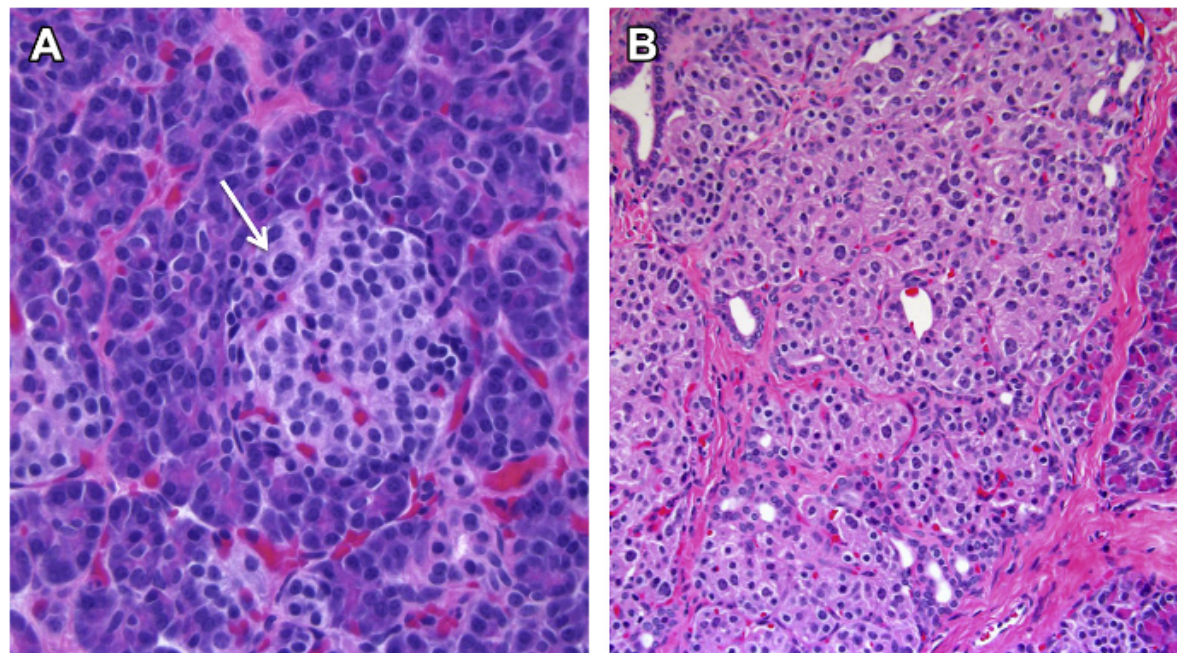


Fig. 2. (A) Section of pancreas from a diffuse case showing a pancreatic islet demonstrating β -cell nucleomegaly (*white arrow*), histologic hallmark of diffuse disease (H&E, original magnification $\times 400$). (B) Adenomatous lesion from a case of focal HI (H&E, original magnification $\times 200$). Normal pancreas tissue is seen on the right side of the image.

Mariko et al., Congenital Hyperinsulinism: Intraoperative Biopsy Interpretation Can Direct the Extent of Pancreatectomy. Am J Surg Pathol 2004; 28(10):1326-1335. doi: 10.1097/01.pas.0000138000.61897.32

Diffuse form on frozen section, nucleomegaly

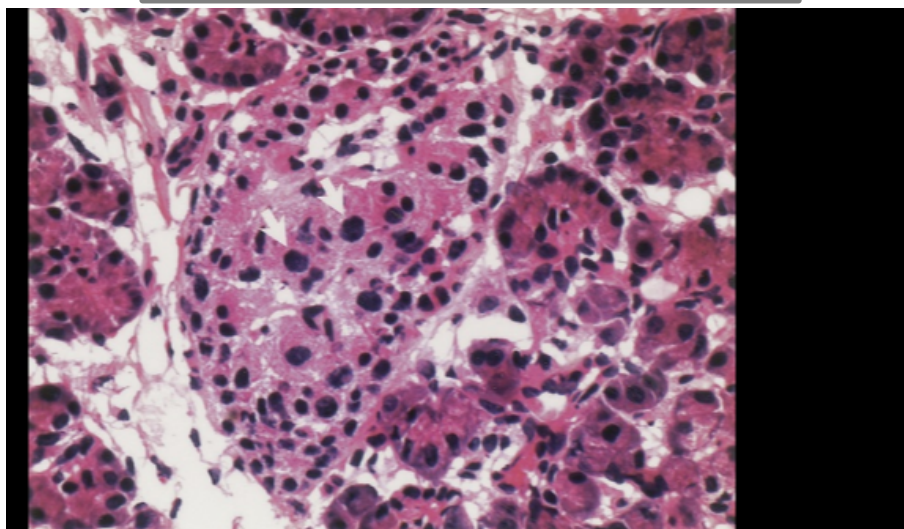


FIGURE 3.

Frozen section photomicrograph of diffuse form of hyperinsulinism (case 7). Large islet cell nuclei at least 3 times larger than the surrounding endocrine cell nuclei (arrows) are present. (Hematoxylin and eosin stain. Original magnification $\times 400$).

Source

Congenital Hyperinsulinism: Intraoperative Biopsy Interpretation Can Direct the Extent of Pancreatectomy