Endocrine Manifestations of Langerhans Cell Histiocytosis

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Introduction

Langerhans cell histiocytosis (LCH) is a rare granulomatous and proliferative disease. Clinical presentation and aggressiveness are very heterogeneous, extending from very benign to disseminated forms, that causes significant mortality. Indeed, LCH aggregates in one entity a group of diseases characterized by clonal proliferation and/or accumulation of cells phenotypically similar to cutaneous Langerhans cells (surface markers and ultrastructure). Multisystem forms frequently have hypothalamo–pituitary axis involvement.

Clinical Case 1

A 15-year-old Caucasian woman presented with a 14-month history of headaches, secondary amenorrhea. She reported polyuria and polydipsia in the last 2 years.

Analyte	Result	Reference
Glucose	88	60-109 mg/dL
Creatinine*	0.9	0.66-1.09 mg/dL
Na+	144	136-146 mmol/L
K+	4.1	3.5-5.1 mmol/L
Osmolality*	287	260-302 mOSM/kg
IGF-1	341	183-996 ng/mL
PRL	66	< 20 ng/mL
TSH	1.1	0.4-4 µUI/mL
FT3	297	230-530 pg/%
FT4	0.6	0.78-1.94 ng/%
FSH	<0.07	µUI/mL
LH	<0.07	µUI/mL
E2	14	pg/mL
Progesterone	0.9	ng/mL

* - Serum analytes

Insulin Tolerance Test

Time (minutes)	Glucose (mg/dL)	ACTH (pg/mL)	Cortisol (µg/dL)	GH (µUI/L)
0	87	43	18	0.3
15	41	27	16	0.3
30	18	33	15	0.4
45	55	99	21	0.3
60	70	67	22	0.2
90	81	30	15	0.2
120	90	26	11	0.2

TRH Test

Time (minutes)	TSH (µUI/mL)	FT4 (ng/%)	FT3 (pg/%)
0	1.1	0.6	297
20	7.8		
60	8.4		

GnRH Test

Time (minutes)	LH (µUI/mL)	FSH (µUI/mL)
0	<0.07	<0.07
20	0.4	0.9
60	0.5	2.8

Imaging: hypothalamic mass of 10 mm

Pituitary transcranial surgery

After surgery: **panhypopituitarism**

- Levothyroxine 50 µg *id*
- Ethinylestradiol 0,03 mg gestodene 0.075 mg *id*
- Desmopressin 0.1 mg/mL *id*
- Hydrocortisone 5 mg *id*

Histology: inconclusive

9 monts after surgery...

MRI: hypothalamic residue of 14x12.8 mm

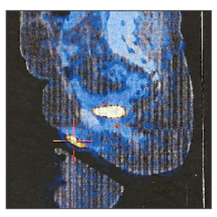
Adjuvant radiotherapy (54Gy)

3 years after surgery...

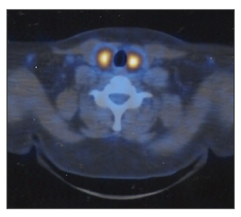
Patient reported a 16-month history of vulvar ulceration, to which she had been submitted to three surgical excision procedures in the previous year.

Vulvar Histology: Langerhans Cell Histiocytosis

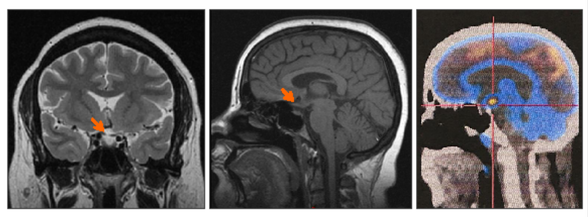
Vulva



Thyroid



Hypothalamo-Pituitary Axis



Vulvar radiotherapy (10 Gy)
Prednisolone/Methotrexate/Vimblastine
Endocrine substitutive Rx

- Levothyroxine 50 µg *id*
- Ethinylestradiol 0,03 mg gestodene 0.075 mg *id*
- Desmopressin 0.1 mg/mL *id*
- Hydrocortisone 5 mg *id*

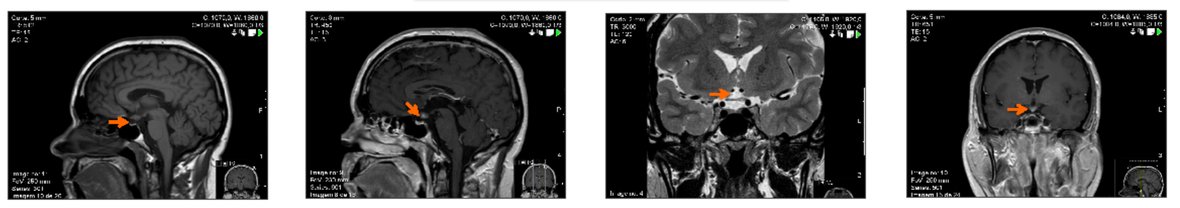
Complete Remission

Permanent endocrine deficits

Clinical Case 2

A 37-year-old Caucasian man presented with a 6-month history of otalgy, otorrhea, weight loss, and brown maculo-papular skin rash. He reported polyuria, and polydipsia in the previous 5 years. Recently he noted vision impairment. A mass in the temporal bone was found. Imaging studies revealed osteolytic lesions in the temporal bone and a 2 cm suprasellar mass.

Hypothalamo-Pituitary Axis



Analyte	Result	Reference
Glucose	77	60-109 mg/dL
Creatinine*	0.8	0.66-1.09 mg/dL
Na+	137	136-146 mmol/L
K+	4.5	3.5-5.1 mmol/L
Osmolality*	272	260-302 mOSM/kg
IGF-1	26	109-284 ng/mL
PRL	38	< 18 ng/mL
TSH	1.8	0.4-4 µUI/mL
FT3	148	230-530 pg/%
FT4	0.6	0.78-1.94 ng/%
FSH	<0.3	< 15µUI/mL
LH	<0.1	<9 µUI/mL
Total Testosterone	<0.1	2.7-11 ng/mL
Free Testosterone	0.8	13-40 pg/mL

* - Serum analytes

TRH Test

Time (minutes)	TSH (µUI/mL)	FT4 (ng/%)	FT3 (pg/%)
0	1.8	0.6	148
20	7.9		
60	6.9		

GnRH Test

Time (minutes)	LH (µUI/mL)	FSH (µUI/mL)
0	<0.1	<0.3
20	0.1	1.3
60	0.1	1.0

ACTH Stimulation Test

Time (minutes)	Cortisol (µg/dL)	ACTH (pg/mL)
0	3.2	15
60	16	

Temporal Bone Histology: Langerhans Cell Histiocytosis

Prednisolone/Methotrexate/Vimblastine
Endocrine substitutive Rx

- Desmopressin 0.1 mg *id*
- Levothyroxine 100 µg *id*
- Hydrocortisone 10mg + 5mg + 5mg
- Testosterone 250 mg each 3 weeks

Complete Remission

Permanent endocrine deficits

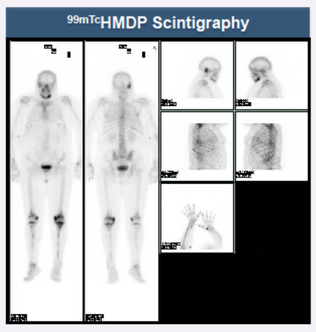
Clinical Case 3

A 60-year-old Caucasian woman presented with 6-month history of jaw pain and weight loss. Secondary evaluation revealed polyostotic Langerhans cell histiocytosis and the patient was treated with zoledronic acid. Three years later she complained of headaches, polyuria and polydipsia. MRI revealed pituitary stalk enlargement.

Analyte	Result	Reference
Glucose	80	60-109 mg/dL
Creatinine*	0.75	0.66-1.09 mg/dL
Na+	140	136-146 mmol/L
K+	4.1	3.5-5.1 mmol/L
Osmolality*	277	260-302 mOSM/kg
IGF-1	135	81-225 ng/mL
PRL	35	< 20 ng/mL
TSH	5.0	0.4-4 µUI/mL
FT3	2.4	1.8-4.2 pg/mL
FT4	0.7	0.8-1.9 ng/dL
FSH	2.5	µUI/mL
LH	1.3	µUI/mL
E2	20	pg/mL
Progesterone	0.4	ng/mL

* - Serum analytes

^{99m}Tc-HMDP Scintigraphy



ACTH Stimulation Test

Time (minutes)	Cortisol (µg/dL)	ACTH (pg/mL)
0	3.2	15
60	16	

Prednisolone/Vimblastine
Endocrine substitutive Rx

- Desmopressin 0.1 mg id
- Levothyroxine 100 µg *id*

Conclusion

- All cases described had hypothalamo-pituitary axis involvement with pituitary failure. The dominant manifestation was diabetes insipidus.
- If not treated promptly LCH may have a considerable morbi-mortality with permanent endocrine failures, that require proper hormonal substitution. Relapses may occur and appropriate follow-up is recommended.

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Pituitary clinical
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