Case Report

A COMMON PITUITARY AUTOANTIBODY IN TWO PATIENTS WITH IMMUNE CHECKPOINT INHIBITOR-MEDIATED HYPOPHYSITIS: ZCCHC8

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ABSTRACT

Objective: Hypophysitis is an increasingly recognized adverse effect of immune checkpoint inhibitor (ICI) therapy for malignancy. However, the mechanisms through which ICIs induce hypophysitis are largely unknown. We aim to describe 2 cases of ICI-mediated hypophysitis and perform autoantibody profiling on serial samples from these patients to determine if common autoantibodies could be identified.

Methods: We describe 2 cases of patients with metastatic urothelial cancer who received ICI therapy and subsequently developed severe fatigue, prompting a hormonal workup consistent with hypopituitarism. Patient 1 received the ICI ipilimumab (anti-cytotoxic T-lymphocyte-associated protein 4) and patient 2 received the ICI pembrolizumab (anti-programmed cell death protein 1). Both patients had serial seromic immune biomarker profiling using high-density protein arrays before and after developing hypophysitis. Once a common autoantibody was found, zinc finger CCHC-type containing 8 (ZCCHC8), we used immunohistochemistry to assess its presence in pituitary tissue.

Results: Of a limited number of increased autoantibodies detected, those to ZCCHC8 were the only common antibodies to increase at least 3-fold post-hypophysitis in both patients. Using immunohistochemistry staining, we show for the first time that ZCCHC8 is expressed in pituitary gland tissue.

Conclusion: Seromic profiling identified a common autoantibody, ZCCHC8, in 2 patients who developed hypophysitis on ICI therapy, and other serial autoantibody increases in each patient. These findings warrant validation in other cohorts to determine if the response is to self or tumor antigen, and may reveal novel insights into pituitary gland physiology and the pathogenesis of ICI-mediated hypophysitis. **(AACE Clinical Case Rep. 2020;6:e151-e160)**

Abbreviations:
ACTH = adrenocorticotropic hormone; **BSA** = bovine serum albumin; **fT4** = free thyroxine; **ICI** = immune checkpoint inhibitor; **TSH** = thyroid-stimulating hormone; **ZCCHC8** = zinc finger CCHC-type containing 8

INTRODUCTION

Hypophysitis is a rare, but increasingly recognized immune-mediated adverse event associated with immune checkpoint inhibitor (ICI) cancer therapy. By blocking the cytotoxic T-lymphocyte antigen 4 pathway as well as the programmed cell death protein 1 and programmed cell death ligand protein 1 checkpoint pathways, ICIs augment immune responses against cancer cells (1). ICIs also can induce an immune response to host cells, leading to immune-mediated adverse events such as hypophysitis (2). The incidence of hypophysitis in clinical trials has been reported as 0.5 to 18% (3).

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The role of autoantibodies in patients with ICI-mediated hypophysitis is largely unknown. Autoantibodies are required to help T cells develop and have a possible pathogenic role in the development of hypophysitis and other ICI-mediated adverse events (1,2). Proteome arrays are a tool to profile thousands of autoantibodies against many unique human antigens simultaneously. These arrays identify patterns of autoantibody response against a large number of antigens during the course of development of diseases, such as autoimmunity or malignancy (4-6). Protoarray studies have shown that certain autoantibodies may predict ICI toxicity (7,8), but only one recent study has examined autoantibody changes in hypophysitis specifically, showing increases in the autoantibodies GNAL and ITM2B in 8 patients (including melanoma, prostate cancer, and renal cell carcinoma) (9).

In this report, our objective is to describe 2 cases of ICI-mediated hypophysitis, with one patient on ipilimumab (anti-cytotoxic T-lymphocyte-associated protein 4 monoclonal antibody) and the other patient on pembrolizumab (anti-programmed cell death protein 1 monoclonal antibody) and perform autoantibody profiling on serial samples from these patients to determine if common autoantibodies could be identified. Once common autoantibodies to the zinc finger CCHC-type containing 8 (ZCCHC8) protein were identified, we also aimed to determine if ZCCHC8 is expressed in pituitary tissue.

CASE REPORT

Case 1

A 75-year-old woman with a past history of metastatic urothelial carcinoma was enrolled in a clinical trial of gemcitabine, cisplatin, and ipilimumab as first line treatment for metastatic urothelial carcinoma (Fig. 1 *A*). Ipilimumab treatment (10 mg/kg) was started after receiving 6 weeks of treatment with gemcitabine and cisplatin. The patient received 8 weeks of ipilimumab with a computed tomography scan showing complete radiologic response of disease after completing treatment.

One month after completing ipilimumab, the patient developed fatigue and headaches. These symptoms prompted a magnetic resonance imaging scan that showed a 7.2 × 6.9-mm enhancing pituitary nodule. Further workup (Table 1) showed laboratory values that were consistent with hypopituitarism, including thyroid-stimulating hormone (TSH) of 0.07 IU/mL (reference range is 0.4 to 4.2 IU/mL), free thyroxine (fT4) of 1.07 ng/dL (reference range is 0.8 to 1.5 ng/dL), morning cortisol of 0.7 μg/dL (reference range is 6.7 to 22.6 μg/dL), adrenocorticotropic hormone <10 pg/mL (reference range is 0 to 46 pg/mL), follicle-stimulating hormone of 12.6 mIU/mL (reference range is 16.7 to 113.6 mIU/mL), luteinizing hormone of 5.1 mIU/mL (reference range is 10.9 to 58.6 mIU/mL), and prolactin of 22.7 ng/mL (reference range is 2.7 to 19.6 ng/mL). The patient was started on prednisone with improvement in symptoms. Approximately 5 weeks later, due to symptoms of fatigue and constipation, she was started on levothyroxine for hypothyroidism. Three months after developing hypophysitis, the patient's metastatic urothelial cancer progressed.

Case 2

A 75-year-old man with a history of metastatic urothelial cancer progressive on chemotherapy received pembrolizumab (Fig. 1 *B*). After completing 4 cycles of pembrolizumab at 200 mg, the patient had no evidence of disease progression. TSH and fT4 levels at the time were suggestive of central hypothyroidism with TSH at 0.11 IU/mL and fT4 at 0.74 ng/dL. Laboratory workup at the time demonstrated hypogonadotropic hypogonadism (Table 2). Pituitary hormones were checked showing random cortisol of 21 μg/dL, ACTH at 54 pg/mL, total testosterone at 76.42 ng/dL (reference range is 300 to 180 ng/dL), follicle-stimulating hormone at 5.6 mIU/mL (reference range is 1.3 to 19.3 mIU/mL), luteinizing hormone at 2.21 mIU/mL (reference range is 1.2 to 8.6 mIU/mL), and prolactin at 2.9 ng/mL (reference range is 2.6 to 13.1 ng/mL).

Three weeks later, the patient had severe fatigue and was found to have a random cortisol of 3 μg/dL, ACTH of 13 pg/mL, TSH of 0.008 IU/mL, and fT4 of 0.92 ng/dL. He started high-dose prednisone and levothyroxine. After fatigue symptoms resolved on treatment, he resumed pembrolizumab without further complications and without progression of urothelial cancer.

Materials and Methods

The patient samples used in this analysis were stored as part of a bladder cancer repository. Both patients provided informed consent to have their samples banked for research purposes via a protocol approved by our institutional review board (IRB # 10-1180).

Our laboratory previously validated protein array assays by comparing them to enzyme-linked immunosorbent assay antibody testing (10), as well as established normalization and calculation techniques (11). ProtoArray Human Protein Microarrays v5.1 (Thermo Fisher Scientific, Waltham, MA) were used to profile circulating antibodies against approximately 9,000 antigens (including controls) spotted in duplicate with the same methodology as done in prior studies by our laboratory (4). Median relative fluorescent unit values from the arrays were quantile normalized between the 3 time points available from each patient, as previously described with minor adjustments, namely without performing interquartile calculations (11). A fold difference >2.5 times baseline was considered significant. ZCCHC8 expression was evaluated by immunohistochemistry staining of normal pituitary glands, pituitary tumors,

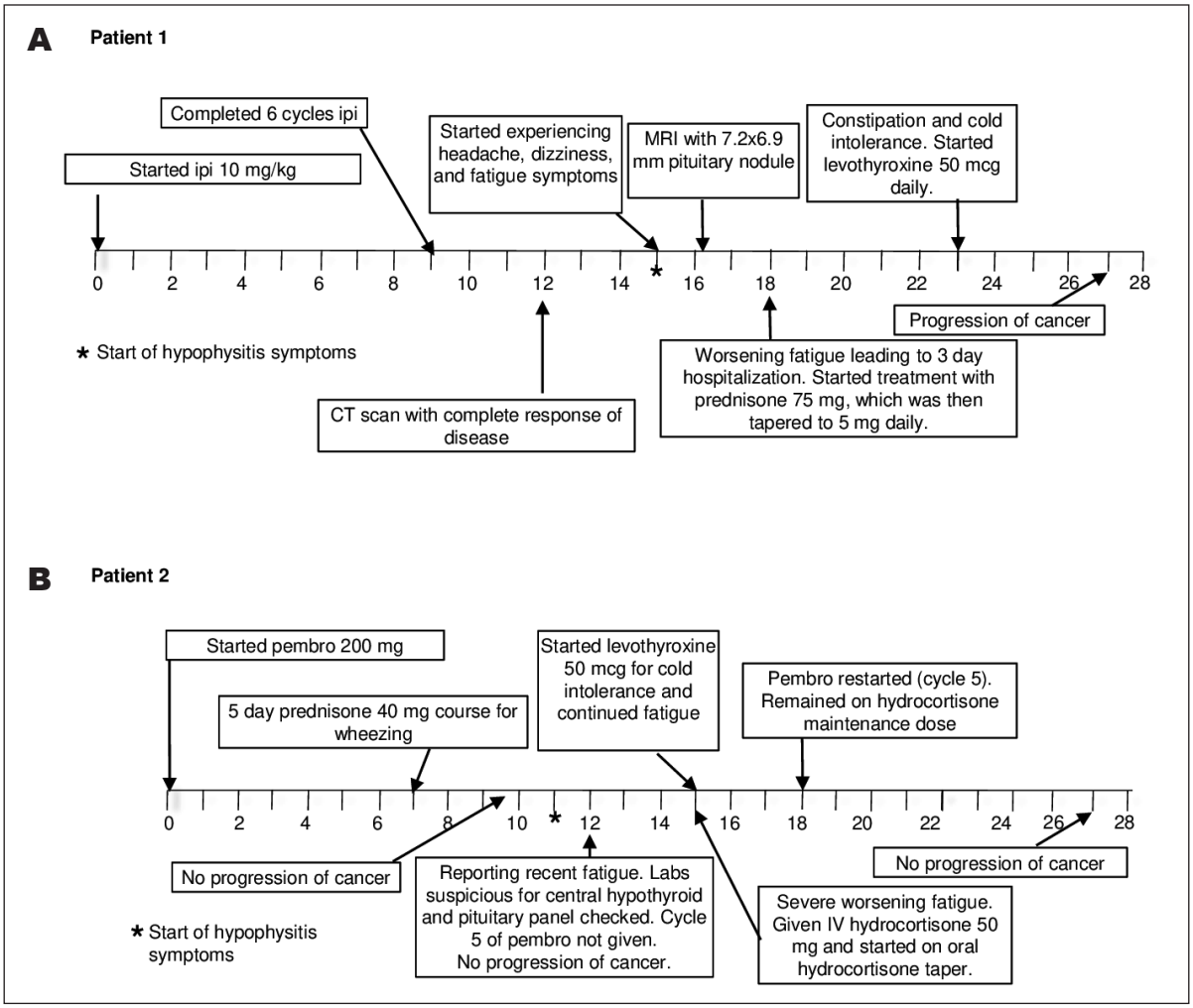

Fig. 1. Timelines of the patients' events in weeks. (*A*) Timeline of patient 1's relevant clinical events after initiating ipilimimuab (ipi). (*B*) Timeline of patient 2's relevant clinical events after starting pembrolizumab (pembro).

Table 1
Patient 1 Pituitary Laboratory Values

	Reference range	0 weeks	9 weeks	18 weeks	23 weeks
Thyroid-stimulating hormone (IU/mL)	0.40-4.20	1.79	0.74	0.07	0.45
Free thyroxine (ng/dL)	0.8-1.5	N/A	N/A	1.00	N/A
Total triiodothyronine (pg/mL)	87-178	N/A	N/A	153	N/A
Morning cortisol (μg/dL)	6.7-22.6	N/A	N/A	0.7	N/A
Adrenocorticotropic hormone (pg/mL)	0-46	N/A	N/A	<10	<10
Follicle-stimulating hormone (mIU/mL)	16.7-113.6	N/A	N/A	12.6	N/A
Luteinizing hormone (mIU/mL)	10.9-58.6	N/A	N/A	5.1	N/A
Prolactin (ng/mL)	2.7-19.6	N/A	N/A	22.7	N/A
Abbreviation: N/A = not available.					

Table 2
Patient 2 Pituitary Laboratory Values

	Reference range	0 weeks	3 weeks	9 weeks	12 weeks	12.5 weeks	25 weeks	27 weeks
Thyroid-stimulating hormone (IU/mL)	0.40-4.20	0.44	0.15	0.07	0.11	N/A	0.01	N/A
Free thyroxine (ng/dL)	0.80-1.50	0.92	0.82	0.69	0.74	N/A	0.92	N/A
Free triiodothyronine (pg/mL)	2.50-3.90	3.00	2.03	1.28	1.75	N/A	2.42	N/A
Random cortisol (μg/dL)	6.7-22.6	N/A	N/A	N/A	N/A	21.0	3.0	N/A
Adrenocorticotropic hormone (pg/mL)	0-46	N/A	N/A	N/A	<10	N/A	13	<5
Follicle-stimulating hormone (mIU/mL)	16.7-113.6	N/A	N/A	N/A	N/A	5.6	N/A	N/A
Luteinizing hormone (mIU/mL)	10.9-58.6	N/A	N/A	N/A	N/A	2.2	N/A	N/A
Prolactin (ng/mL)	2.7-19.6	N/A	N/A	N/A	N/A	2.9	N/A	N/A
Testosterone (ng/dL)	300-1080	N/A	N/A	N/A	N/A	76	N/A	N/A

Abbreviation: N/A = not available.

and testis (positive control) obtained at autopsy at our institution (IRB exempt). Antibodies used for staining were total ZCCHC8 (PA5-57969, Thermo Fisher Scientific) at 1:50 dilution. ZCCHC8 was detected using the rabbit HRP/DAB micro-polymer detection kit (Abcam, Cambridge, United Kingdom).

Results

Both patients had autoantibodies with significant fold change increases before and after hypophysitis. Patient 1 had increases in autoantibodies against 93 specific proteins between weeks 0 and 23 (Fig. 2 *A* and Table 3). Patient 2 had autoantibodies against 21 specific proteins between weeks 2 and 12 (Fig. 2 *B* and Table 4). Some autoantibodies also peaked prior to developing hypophysitis in both patients: 23 in patient 1 (Table 5) and 3 in patient 2 (Table 6). ZCCHC8 was the only common protein for which autoantibodies were found to be significantly increased after both patients developed hypophysitis. Of note, patient 1 had an increased response to control protein bovine serum albumin (BSA), though less than other reported antigens. In serum and plasma, >90% of analytes were similar and coefficients of variation for each patient were lower than the coefficients of variation observed when comparing plasma to each other or sera to each other, showing that the greater driving factor for reactivity was due to patient differences rather than specimen type (Fig. 3).

Immunohistochemical staining demonstrated that ZCCHC8 was expressed in pituitary tissue and ACTH-secreting pituitary tumor tissue (Fig. 4 *A* through *C*). Blood vessels in the pituitary slides did not stain for ZCCHC8, serving as an internal negative control. ZCCHC8 localized to the nucleus. ZCCHC8 was also expressed in testis (Fig. 4 *D*), as previously reported, and was used as a positive control in this experiment (12).

DISCUSSION

Proteome array identified a common autoantibody, ZCCHC8, in 2 patients who developed hypophysitis on ICI therapy. Immunohistochemistry staining revealed that ZCCHC8 is expressed in normal and ACTH-secreting pituitary tissue. ZCCHC8 is a zinc-knuckle protein known to be involved in cellular RNA processing (13). Gene expression studies have confirmed ZCCHC8 is present in the pituitary gland at the mRNA level (12), though its role in pituitary physiology is unknown. To our knowledge, until this study, protein expression of ZCCHC8 specifically in pituitary tissue had never been studied. Expression of ZCCHC8 has been shown in urothelial carcinoma (12).

Proteome array techniques have identified novel autoantibodies in autoimmune endocrine entities such as autoimmune polyendocrine syndrome 1 (5) and type 1 diabetes mellitus (6). In regard to ICI-mediated hypophysitis, one study showed serial increases in autoantibodies to the proteins GNAL and ITM2B in patients treated with ipilimumab. ZCCHC8 autoantibodies were not increased in this discovery cohort (9). Our study showed that patient 1 had a 2.4-fold increase in ITM2B and patient 2 had no ITM2B increases. GNAL was not part of our protoarray panel. The differences between our studies may suggest different autoantibody profiles in different malignancy types and different hypophysitis mechanisms. To our knowledge, our case series is the first to publish findings on autoantibodies in patients with ICI-mediated hypophysitis with urothelial cancer and the first to show that ZCCHC8 is expressed in pituitary tissue.

Our results must be interpreted with caution, as there are many limitations to our report. In our protoarray assays, we used both patient sera and plasma (Fig. 2). Across sera and plasma, the vast majority of analytes were similar and

work pending publication in our lab has shown concordance in serum and plasma to multiple tumor antigens. Additionally, lack of a control group further impairs our autoantibody testing interpretation, as we cannot know if increased autoantibodies are to tumor or to self-antigens, or if preexisting antibodies may play a role in pathogenesis. Furthermore, patient 2 did not have a week 0 timepoint and patient 1 had more autoantibody increases than patient 2, including to the control antigen BSA. Anti-BSA antibodies may have clinical relevance, as they have been seen in patients with autoimmune conditions (14,15). Although this could lead to some false positive results due to protein preparation, the fold change in reported autoantibodies were all higher than those seen against BSA.

CONCLUSION

The finding of increased autoantibodies in patients with ICI-mediated hypophysitis warrants validation in other cohorts to determine if the response is to self or tumor antigen and may reveal insights into pituitary physiology and predictors of ICI-mediated hypophysitis. Future studies should include proteome assay autoantibody testing in a control population and a larger cohort

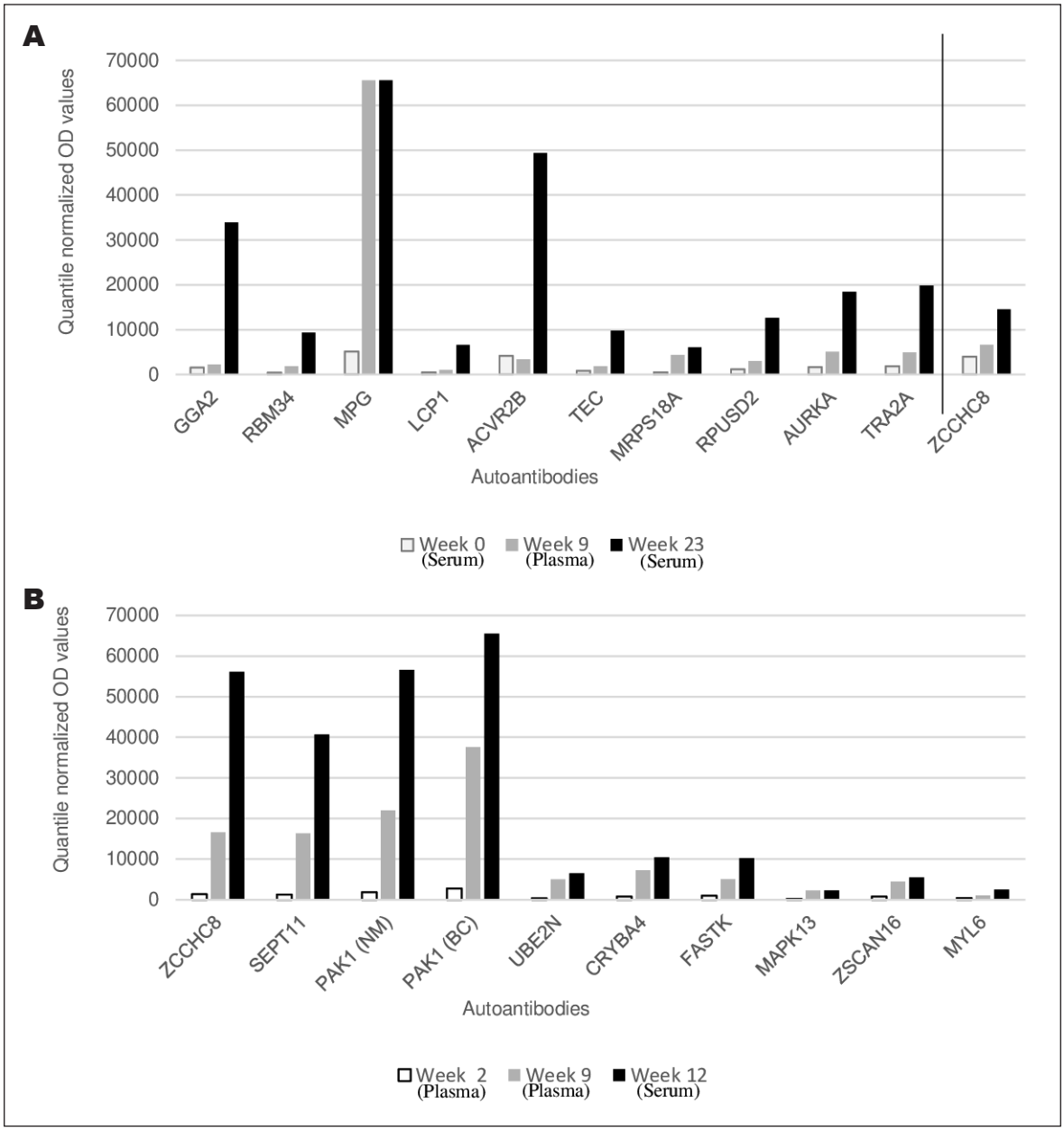

Fig. 2. The 10 autoantibodies with the highest fold increases post-hypophysitis and ZCCHC8. (*A*) Quantile normalized fluorescent optical density values in patient 1 pre-hypophysitis (weeks 0 and 9) and post-hypophysitis (week 23). (*B*) Quantile normalized optical density values in patient 2 pre-hypophysitis (weeks 2 and 9) and post-hypophysitis (week 12).

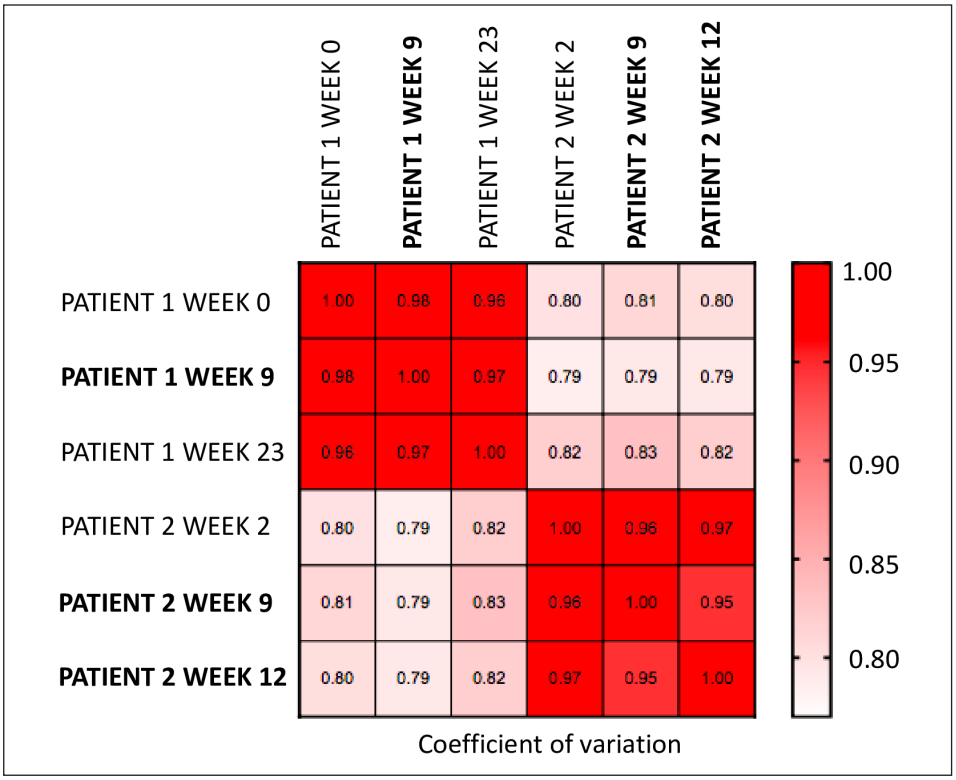

Fig. 3. Non-parametric Spearman correlation matrix of the fluorescent optical density data after quantile normalization. Bolded text is plasma sample and normal text is serum sample.

Table 3
Patient 1 Autoantibody Gene Loci with ≥2.5 Peak Fold Increases Post-Hypophysitis

		Quantile normalized optical density values			
	Gene symbol	**Week 0**	**Week 9**	**Week 23**	**Ratio week 23 to week 0**
BC000284.1	*GGA2*	1571	2256	33890	21.6
NM_015014.1	*RBM34*	486	1853	9332	19.2
BC014991.1	*MPG*	5159	65535	65535	12.7
NM_002298.2	*LCP1*	541	1038	6545	12.1
BC096245.1	*ACVR2B*	4196	3428	49378	11.8
NM_003215.1	*TEC*	859	1860	9777	11.4
NM_018135.2	*MRPS18A*	548	4403	6083	11.1
NM_152260.1	*RPUSD2*	1139	3053	12619	11.1
NM_003600.1	*AURKA*	1710	5088	18425	10.8
NM_013293.1	*TRA2A*	1846	4948	19825	10.7
BC096243.1	*ACVR2B*	1218	925	11859	9.7
NM_003959.1	*HIP1R*	2324	8934	21092	9.1
BC048299.1	*SPATS2*	1471	6323	13304	9.0
NM_001798.2	*CDK2*	427	978	3771	8.8
NM_016304.2	*C15orf15*	1638	5552	14388	8.8
BC034718.1	*EPB41L2*	2078	7511	17692	8.5
NM_015138.2	*RTF1*	1267	973	10297	8.1

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Table 3 *Continued*					
NM_021803.1	*IL21*	668	1508	5100	7.6
NM_000899.3	*KITLG*	1894	13873	14229	7.5
BC011600.1	-	2193	14358	16358	7.5
NM_002391.1	*MDK*	1076	2366	8003	7.4
BC028059.1	*TPSAB1*	1884	4789	13119	7.0
NM_004216.2	*DEDD*	721	2318	4923	6.8
NM_002904.4	*RDBP*	2951	14954	19733	6.7
NM_198467.1	*RSBN1L*	483	1084	3189	6.6
NM_032848.1	*C12orf52*	2089	5222	13715	6.6
NM_002378.2	*MATK*	872	3576	5657	6.5
NM_012473.2	*TXN2*	1526	4315	9799	6.4
NM_005409.3	*CXCL11*	1366	7748	8771	6.4
AAH19931.1	*FCGR2A*	3060	7632	19487	6.4
NM_032141.1	*CCDC55*	2872	17943	17983	6.3
NM_018553.1	*C17orf85*	1126	2458	7045	6.3
NM_080390.3	*TCEAL2*	5821	10830	36228	6.2
NM_003215.1	*TEC*	1913	3485	11148	5.8
BC001304.1	*PCLO*	4089	16941	22119	5.4
BC067085.1	*HIP1R*	5886	11949	31115	5.3
BC070073.1	*ZNF365*	847	3341	4330	5.1
NM_033453.2	*ITPA*	988	4980	5039	5.1
NM_001896.1	*CSNK2A2*	1705	3317	8686	5.1
NM_033293.1	*CASP1*	256	411	1272	5.0
NM_207480.1	*UNQ5830*	1406	2997	6869	4.9
BC040020.2	*SUHW2*	2594	5657	12675	4.9
BC013796.1	*AP2M1*	540	1610	2612	4.8
NM_012148.1	*DUX3*	2112	3950	10126	4.8
NP_000600.1	*CXCL12*	2374	7089	11170	4.7
BC059174.1	*TRAF3IP1*	2191	14878	10280	4.7
BC000770.1	*DIDO1*	3298	5904	15443	4.7
NM_022551.2	*RPS18*	1028	2103	4733	4.6
BC005043.1	*TNFRSF10C*	3860	12750	17339	4.5
BC003049.1	*SERBP1*	3382	11276	15171	4.5
NM_014481.2	*APEX2*	9890	39513	44263	4.5
NM_006799.2	*PRSS21*	592	1854	2645	4.5
NM_003677.3	*DENR*	637	1149	2837	4.5
NM_000975.2	*RPL11*	589	1663	2617	4.4
BC000903.2	*HMGB2*	1058	2242	4638	4.4
NM_004728.2	*DDX21*	1617	24396	7089	4.4
NM_002690.1	*POLB*	1080	2603	4712	4.4
NM_207285.1	*AAA1*	3311	6228	14439	4.4
NM_012341.2	*GTPBP4*	1487	5111	6472	4.4
NM_031417.1	*MARK4*	791	2927	3402	4.3
BC023569.1	*UPF3A*	2724	5106	11702	4.3

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Table 3 *Continued*					
BC093990.1	*SUDS3*	3738	4843	15965	4.3
BC060845.1	*L3MBTL3*	566	603	2364	4.2
BC020555.1	*SERBP1*	2779	8792	11616	4.2
NM_001029.2	*RPS26*	978	1072	4075	4.2
BC011842.2	*FLJ11184*	1831	5767	7621	4.2
BC014774.1	*BAG1*	1210	1601	4926	4.1
BC032508.1	*FLJ10781*	1035	1817	4196	4.1
NM_006275.2	*SFRS6*	711	1153	2883	4.1
BC015505.1	*DDX42*	3751	6554	15150	4.0
NM_080548.1	*PTPN6*	1116	2235	4479	4.0
BC013005.2	*IK*	482	1278	1921	4.0
NM_133336.1	*WHSC1*	471	1398	1874	4.0
BC010907.1	*PAK1IP1*	710	1329	2822	4.0
NM_198081.1	*SCML4*	1053	5168	4125	3.9
BC029796.1	*LOC116349*	5168	8927	19970	3.9
NM_015634.2	*KIAA1279*	920	2971	3543	3.9
BC096708.1	*WIT1*	4280	7533	16256	3.8
NM_002103.3	*GYS1*	1247	4040	4671	3.7
NM_014303.2	*PES1*	1448	4542	5394	3.7
NM_017612.1	*ZCCHC8*	3970	6640	14505	3.7
NM_006658.1	*C7orf16*	4176	10482	15215	3.6
NM_199124.1	*C11orf63*	4199	13185	15259	3.6
NM_015891.2	*CDC40*	3341	5952	12100	3.6
BC099907.1	*GTF2I*	8025	37447	28856	3.6
NM_003583.2	*DYRK2*	1161	6398	3912	3.4
NM_138730.1	*HMGN3*	1678	6683	5088	3.0
NM_201998.1	*SF1*	9401	36764	27587	2.9
NM_004103.2	*PTK2B*	789	3607	2237	2.8
BC015514.1	*TFPI*	2506	11012	6989	2.8
BC063463.1	*COQ3*	710	488	1973	2.8
BC012131.1	*C14orf149*	2554	9927	6693	2.6
NM_005313.3	*PDIA3*	851	10445	2179	2.6

of patients who developed hypophysitis on ICI therapy, as well as further examination of the role of ZCCHC8 in pituitary physiology.

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DISCLOSURE

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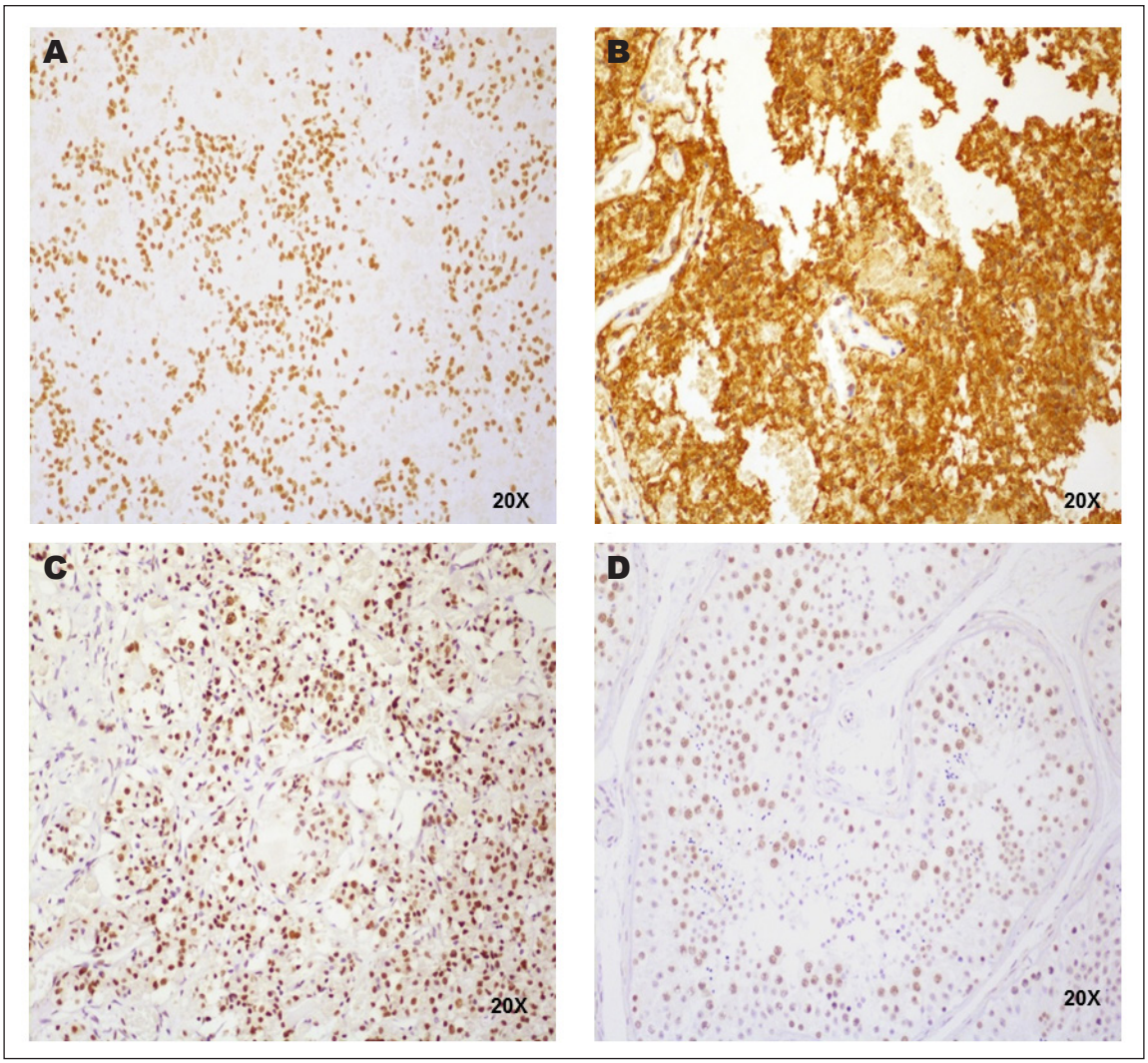

Fig. 4. Immunohistochemical staining. (*A*) Adrenocorticotropic hormone-secreting pituitary adenoma tissue stained for ZCCHC8 (×20). (*B*) Adrenocorticotropic hormone-secreting pituitary adenoma tissue stained for adrenocorticotropic hormone (×20). (*C*) Normal pituitary tissue stained for ZCCHC8 (×20). (*D*) Testis tissue stained for ZCCHC8 (×20).

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