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Cytotoxic T-cell lymphoma with muscle involvement and germline variants in inborn error of immunity-related genes: clinical and genetic insights from a case series

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Peripheral T-cell lymphomas (PTCLs) are a heterogeneous group of mature T-cell and natural killer cell neoplasms with aggressive clinical behavior and poor outcomes [1,2]. Although recurrent somatic mutations involving epigenetic regulation and T-cell receptor signaling have been identified in PTCL [3], the molecular drivers and genetic susceptibility underlying disease development, particularly in young patients, remain incompletely understood.

Inborn errors of immunity are inherited disorders of immune development and function that predispose affected individuals to infections, immune dysregulation, and malignancies, particularly lymphomas [4-8]. Accordingly, there is growing interest in identifying inborn errors of immunity in patients presenting with lymphoid malignancies, and current guidelines recommend genetic screening for pediatric and adolescent cancer patients to uncover underlying immune defects.

Here, we report six young adults with cytotoxic PTCL characterized by prominent skeletal muscle involvement. All patients underwent whole-exome sequencing (WES) using peripheral blood DNA, and peripheral blood smears showed no morphologic evidence of circulating lymphoma cells. Heterozygous variants in inborn error of immunity-related genes were identified in all six cases. Tumor samples from all cases underwent targeted next-generation sequencing (NGS) using a 413-gene panel covering recurrent lymphoma-related genes. We summarize their clinical, pathological, and genetic features and discuss potential links between immune dysregulation and this unusual disease presentation. The study was approved by the institutional review board of Peking Union Medical College Hospital and was done in accordance with the Declaration of Helsinki. Informed consent was obtained from all individual participants included in the study.

Case 1: A 19-year-old male presented with a 1-year history of tongue swelling and a 3-month history of right maxillofacial mass. Progressive tongue enlargement with ulceration and movement restriction was initially responsive to corticosteroids but relapsed after discontinuation. Lower lip biopsy showed dense lymphocytic aggregates in the submucosa. Immunophenotypic findings were consistent with cytotoxic T-cell lymphoma (**Table 1**), and supportive of PTCL-NOS. Clonal T-cell receptor (TCR) Vβ rearrangement was detected by PCR. PET/CT revealed intense ^{18F}-FDG uptake in the oropharynx, cervical lymph nodes, and paraspinal muscles (**Figure 1A**). WES identified heterozygous *UNC13D* c.1352C>T and *STX11* c.401C>G variants. The patient was refractory to CHOP but achieved complete remission after etoposide-based therapy and allogeneic hematopoietic stem cell transplantation (allo-HSCT).

Case 2: A 22-year-old male presented with progressive swelling of the left face and forearm. Biopsies of the upper lip and masseter muscle demonstrated dense lymphocytic infiltration of skeletal muscle fibers, with immunophenotypic findings consistent with cytotoxic T-cell lymphoma. Clonal TCR rearrangement was detected by PCR. PET/CT showed multifocal muscular involvement (SUVmax 25.2; **Figure 1B**). WES revealed a heterozygous *IL7R* c.314G>A mutation. After failure of azacitidine, chidamide, and CHOP, the patient achieved symptom relief with golidocitinib and is scheduled for allo-HSCT.

Case 3: An 18-year-old male presented with eyelid and maxillofacial swelling, fever, and lower limb myalgia. Laboratory tests showed cytopenia. Bone marrow examination revealed

hemophagocytosis. Biopsy of the right buccal mass demonstrated dense lymphocytic infiltration within skeletal muscle fibers with immunophenotypic findings consistent with cytotoxic T-cell lymphoma. Clonal TCR rearrangement was detected by PCR. PET/CT revealed extensive muscular and craniofacial lesions (SUVmax 19.6; **Figure 1C**). A heterozygous *IFIH1* c.229C>T variant was detected. Treatment with golidocitinib plus CHOP induced complete remission, followed by auto-HSCT, with sustained remission.

Case 4: A 20-year-old male had a 5-year history of episodic forearm swelling and fever, followed by progressive facial involvement. He was initially diagnosed with focal myositis and treated with immunosuppressive therapy, with temporary relief. The disease later progressed to involve the orbit, eyelids, and lips, causing swelling, erosion, and trismus. Lip mucosal biopsy showed dense lymphocytic aggregates in the submucosa with a perivascular growth pattern and angioinvasion. Immunophenotypic findings were consistent with cytotoxic T-cell lymphoma and supportive of PTCL-NOS. PET/CT showed diffuse muscular and subcutaneous lesions (SUVmax 35.9; **Figure 1D**). WES identified a heterozygous *LRBA* c.1570G>A mutation. CHOP resulted in partial symptomatic improvement, and he subsequently received supportive treatment.

Case 5: A 16-year-old male presented with progressive lip swelling. Four years earlier, he had been diagnosed with inflammatory myopathy which improved after corticosteroids and immunosuppressive therapy. At the current presentation, he developed bilateral lip swelling. Laboratory tests revealed elevated creatine kinase (CK). Biopsy of the lip mucosa demonstrated focal submucosal lymphocytic infiltration with neurovascular involvement. Immunophenotypic findings were consistent with cytotoxic T-cell lymphoma, and clonal TCR rearrangement was detected by PCR. PET/CT showed diffuse skeletal muscle involvement (SUVmax 30.8; **Figure 1E**). A heterozygous *PRF1* c.1429C>A mutation was detected. The patient achieved complete remission after chidamide plus CHOP and underwent allo-HSCT, remaining in remission.

Case 6: A 19-year-old male presented with mandibular and orbital swelling, fever, and generalized myalgia. One year earlier, he had been diagnosed with autoimmune encephalitis because of recurrent seizures. Laboratory tests revealed elevated LDH and CK levels. Biopsy of the right upper arm muscle demonstrated extensive infiltration by medium-sized lymphocytes with irregular nuclei and mitotic figures within skeletal muscle fibers. Immunophenotypic findings were consistent with cytotoxic T-cell lymphoma, and the pathologic findings supported PTCL-NOS. PET/CT demonstrated diffuse muscular involvement, including the diaphragm (SUVmax 18.3; Figure 1F). WES revealed heterozygous *PRF1* c.1153C>T and UNC13D c.2588G>A mutations. Treatment with golidocitinib plus CHOP resulted in interim complete remission, and therapy is ongoing.

This case series describes a distinctive subset of young patients with cytotoxic phenotype PTCL characterized by predominant skeletal muscle involvement and heterozygous germline variants in inborn error of immunity-related genes. The association between inborn errors of immunity and lymphoid malignancies has been increasingly recognized, with reported cancer risks ranging from 10% to 25% [7, 9]. While B-cell lymphomas are the most commonly reported malignancies in the inborn error of immunity population, T-cell lymphomas occur less frequently. A recent systematic review identified 534 cases of B- and T-cell lymphomas among patients with inborn errors of immunity, of which 74 (13.9%) were T-cell lymphomas [10].

In our cohort, all detected variants were heterozygous and classified as variants of uncertain significance or likely benign, whereas the corresponding syndromes, including FHL, IL7R deficiency, and LRBA deficiency, typically follow an autosomal recessive inheritance pattern and require biallelic mutations for full disease penetrance. Although none of the patients fulfilled diagnostic criteria for a defined syndrome of inborn errors of immunity, several showed clinical or laboratory features suggestive of underlying immune dysregulation, including HLH, hypogammaglobulinemia, prior autoimmune encephalitis, and a prolonged inflammatory/myositis-like course with partial responsiveness to immunosuppressive therapy. These findings support a background of immune dysregulation in this cohort. Because WES was performed on peripheral blood DNA rather than a definitive non-hematopoietic germline source, occult tumor-related contamination cannot be excluded, and the identified variants should therefore be interpreted cautiously. Targeted NGS of tumor samples identified somatic alterations in a subset of cases, including *ARID1A*, *ATRX*, and *STAT5A*. Among these, *ARID1A* and *ATRX* are involved in chromatin remodeling, whereas *STAT5A* is involved in the JAK-STAT signaling pathway. Notably, we did not observe the recurrent epigenetic mutations commonly reported in PTCL, and the overall number of somatic alterations was relatively limited across the cohort, suggesting that this subset may differ from more typical molecular patterns of PTCL.

According to the 2024 IUIS classification, the inborn error of immunity-related genes identified in our cohort span multiple immunological categories, including familial hemophagocytic lymphohistiocytosis-related genes (*UNC13D, STX11*), severe combined immunodeficiency (*IL7R*), and immune dysregulation with autoimmunity due to impaired CTLA-4 trafficking (*LRBA*) [11,12]. Notably, *IFIH1* gain-of-function mutations have been associated with inflammatory myopathies, further supporting a possible link between immune dysregulation and muscle involvement [13]. A striking feature of this series is the predominant involvement of skeletal muscle, an uncommon site for PTCL infiltration. Skeletal muscle has been proposed as a relatively immune-privileged tissue with limited lymphatic drainage and specialized antigen-presenting capacity. In the context of impaired immune regulation, this microenvironment may permit persistent cytotoxic T-cell activation and clonal expansion, thereby providing a niche for lymphomagenesis.

These cases should also be interpreted in the context of the differential diagnosis and the emerging biologic heterogeneity of cytotoxic PTCL. Recent studies have identified biologically distinct subsets of cytotoxic PTCL, including a subgroup characterized by loss of SMARCB1/INI1 expression [14]. Notably, our cases share several features with that subgroup, including young age at onset and cytotoxic phenotype. However, no *SMARCB1* mutations or copy number loss were detected by targeted NGS-based analysis, although SMARCB1/INI1 expression was not evaluated. Therefore, overlap cannot be fully excluded. At the same time, our cases appear distinct from the more typical EBV-associated lymphoproliferative disorders described in the setting of FHL-related defects, as all lesions in this cohort were EBV-negative by EBER in situ hybridization. Another important differential diagnosis is reactive or atypical cytotoxic T-cell proliferation associated with immune dysregulation, because restricted or oligoclonal lymphoid expansions may occur in inborn error of immunity and can complicate interpretation. In our cohort, clonal TCR rearrangement was demonstrated in four cases. The diagnosis was therefore based on integrated clinicopathologic assessment, including morphology, immunophenotype, clonality findings when available, multifocal PET-avid disease, and clinical course. Taken together, these findings suggest that our

cohort may represent a distinct clinicopathologic pattern rather than fitting neatly into currently recognized categories.

In conclusion, we describe a distinctive clinicopathologic pattern of young-onset cytotoxic PTCL with prominent skeletal muscle involvement and inborn error of immunity-related variants. These findings expand the spectrum of PTCL associated with immune dysregulation and suggest that a subset of cases previously regarded as sporadic may arise in the context of subtle inherited immune dysfunction.

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Table 1. Clinical characteristics, immune-related features, treatment, and outcomes of the patients

Patient	Sex/Age	Major clinical symptom	BM and PB	Prior immune disorders	Key lab findings	Pathology features	TCR rearrangement	PIT Score	Treatment and response	Status at last follow-up	Follow-up, months
Case 1	M/19	Painful swelling of the tongue, facial mass	Unremarkable	None	Unremarkable	CD3+, CD5+, CD7+, CD8+, granzyme B+, TIA-1+, EBER-ISH−, Ki-67 80%	Clonal	1	CHOP→SD→allo-HSCT	Alive, ongoing CR	36
Case 2	M/22	Left facial and forearm swelling	Unremarkable	None	Unremarkable	Cytotoxic T-cell phenotype, EBER-ISH−, Ki-67 60%	Clonal	2	Azacitidine and chidamide plus CHOP →SD→golidocitinib	Alive, scheduled for allo-HSCT	25
Case 3	M/18	Eyelid and maxillofacial swelling, fever, lower limb myalgia	HLH and leukopenia	None	Low IgM	Cytotoxic T-cell phenotype, EBER-ISH−, Ki-67 80%	Clonal	1	Golidocitinib plus CHOP→CR→auto-HSCT	Alive, ongoing CR	18
Case 4	M/20	Recurrent fever, forearm swelling, facial/lip swelling	Unremarkable	Focal myositis (5 years earlier)	Elevated CK	Cytotoxic T-cell phenotype, EBER-ISH−, Ki-67 60%	N/A	1	CHOP→not evaluated	Alive, supportive care	9
Case 5	M/16	Progressive lip swelling	Unremarkable	Inflammatory myopathy (3 years earlier)	Elevated CK	Cytotoxic T-cell phenotype, EBER-ISH−, Ki-67 60%	Clonal	1	Chidamide plus CHOP→CR→allo-HSCT	Alive, ongoing CR	9
Case 6	M/19	Mandibular/orbital swelling, fever, diffuse myalgia	Unremarkable	Autoimmune encephalitis (1 year earlier)	Low IgA, IgM, IgG, and elevated CK	Cytotoxic T-cell phenotype, EBER-ISH−, Ki-67 60%	N/A	1	Golidocitinib plus CHOP→CR	Alive, on treatment	6

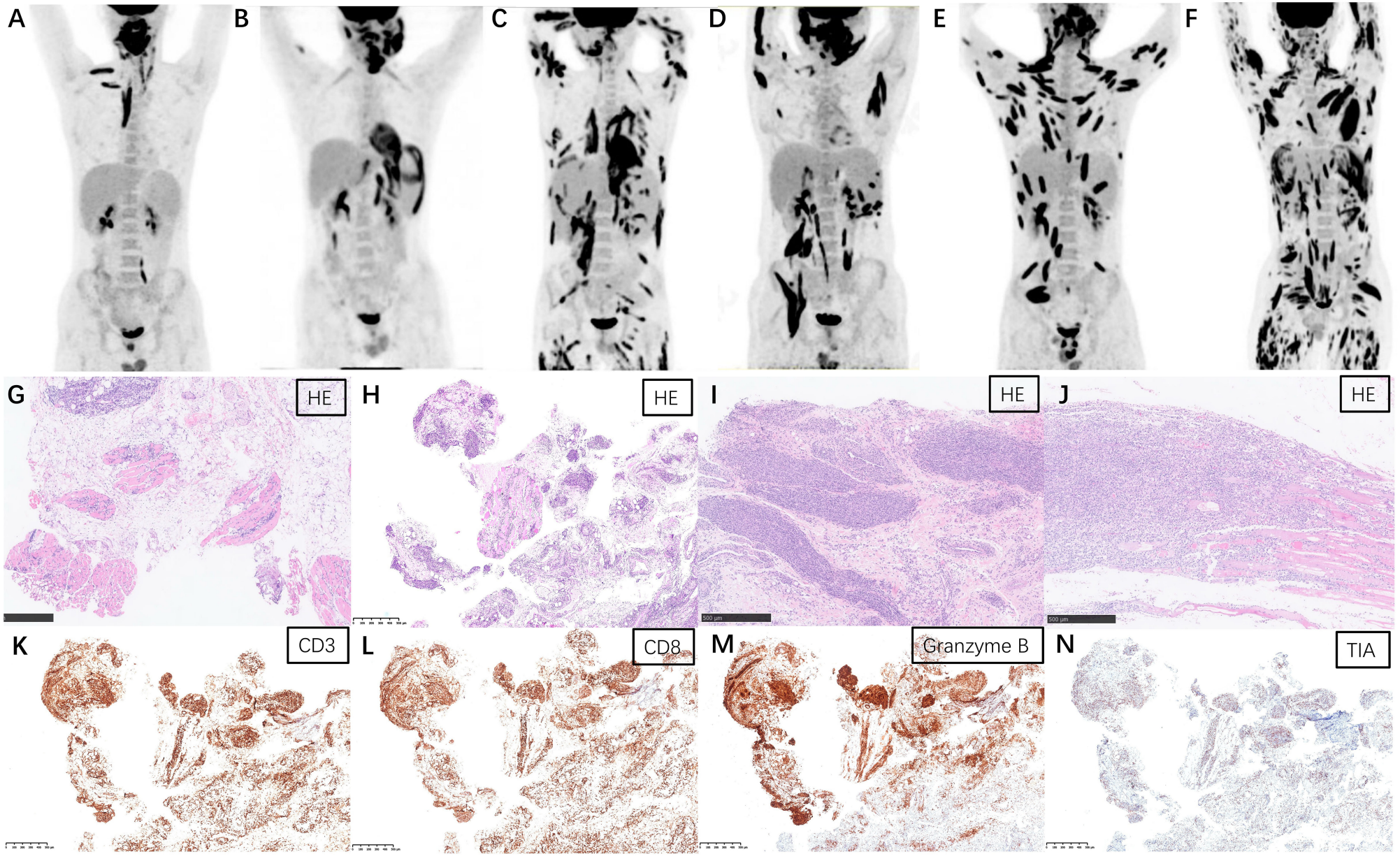
Abbreviations: HLH: hemophagocytic lymphohistiocytosis; BM: bone marrow; PB: peripheral blood. CK: creatine kinase; EBER-ISH: Epstein–Barr virus–encoded RNA in situ hybridization; PIT: prognostic index for PTCL-NOS; CR: complete remission; SD: stable disease; CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone; allo-HSCT: allogeneic hematopoietic stem cell transplantation; auto-HSCT: autologous hematopoietic stem cell transplantation.

Table 2. Variant details and clinical significance

Patient	IEI-related germline mutation	Gene	cDNA/protein change	VAF	Associated IEI condition	ACMG interpretation	SIFT prediction	Somatic mutations in tumor	Somatic mutation types
Case 1	*UNC13D* and *STX11* heterozygous mutations	*UNC13D*	c.1352C>T, p.Thr451Ile	NA	FHL type 3	Uncertain significance	Damaging	ND	
		STX11	c.401C>G, p.Ala134Gly	NA	FHL type 4	Uncertain significance	Tolerated		
Case 2	*IL7R* heterozygous mutation	*IL7R*	c.314G>A, p.Ser105Asn	47%	IL7R deficiency	Uncertain significance	Tolerated	ND	
Case 3	*IFIH1* heterozygous mutation	*IFIH1*	c.229C>T, p.Arg77Trp	48%	MDA5 deficiency	Uncertain significance	Damaging	*ARID1A* c.3458C[2>1]	Frameshift mutation
								ATRX c.2812A>G	Missense mutation
Case 4	*LRBA* heterozygous mutation	*LRBA*	c.1570G>A, p.Gly524Ser	42%	LRBA deficiency	Likely benign	Damaging	ND	
Case 5	*PRF1* heterozygous mutation	*PRF1*	c.1429C>A, p.Pro477Thr	53%	FHL type 2	Uncertain significance	Tolerated	ND	
Case 6	*PRF1* and *UNC13D* heterozygous mutations	*PRF1*	c.1153C>T, p.Arg385Trp	46%	FHL type 2	Uncertain significance	Damaging	*STAT5A* c.2252_2262delAA TTCGACCTG	Frameshift mutation
		UNC13D	c.2588G>A, p.Gly863Asp	50%	FHL type 3	Uncertain significance	Damaging		

Abbreviations: IEI: Inborn errors of immunity; ACMG: American College of Medical Genetics and Genomics; FHL: familial hemophagocytic lymphohistiocytosis; VAF: variant allele frequency; NA: not available; ND: not detected; SIFT: Sorting Intolerant From Tolerant

Figure 1. Representative imaging and histopathologic findings of the cohort. (A–F) Positron emission tomography/computed tomography (PET/CT) images of Cases 1–6, respectively. (G) Hematoxylin and eosin (H&E) staining of the right buccal mass biopsy from Case 3. (H, I) H&E staining of lip biopsies from Cases 4 and 5, respectively. (J) H&E staining of the right upper arm muscle biopsy from Case 6. (K–N) Immunohistochemical staining of the lesion from Case 4 showing positivity for CD3 (K), CD8 (L), granzyme B (M), and TIA-1 (N) (original magnification, ×400).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