

ELANE基因的新型突变Ser126Leu导致先天性中性粒细胞减少症1例

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收稿日期: 2025年2月19日; 录用日期: 2025年3月12日; 发布日期: 2025年3月20日

摘要

重症先天性中性粒细胞减少症(SCN)是一种罕见的血液病,与ELANE基因突变有关。SCN其特征主要是严重中性粒细胞减少合并反复感染,一些SCN患者还可能有口腔表现。我们报告了一名30岁的女性,患有复发性口腔溃疡和严重的慢性牙周炎。全外显子组测序分析显示,她是ELANE上的一种新型错义突变(c.377C > T (p. Ser126Leu))。尽管患者的中性粒细胞绝对值常年浮动于 $0.2 \times 10^9/L$ 上下,但患者18岁后鲜有发生重度感染,因此患者拒绝G-CSF治疗,要求门诊长期随访。本研究针对该病例进行总结分析,旨在提高临床医师对以牙周病变为主要临床表现的重度先天性中性粒细胞减少症的认识。

关键词

ELANE, 先天性中性粒细胞减少症, 牙周病, 口腔溃疡

A Case Report of Novel Mutation in the ELANE Gene Ser126Leu Caused Congenital Neutropenia

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Received: Feb. 19th, 2025; accepted: Mar. 12th, 2025; published: Mar. 20th, 2025

Abstract

Severe Congenital Neutropenia (SCN) is a rare hematologic disorder associated with mutations in

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文章引用: 刘美婷, 王华芳. ELANE 基因的新型突变 Ser126Leu 导致先天性中性粒细胞减少症 1 例[J]. 临床医学进展, 2025, 15(3): 1860-1864. DOI: 10.12677/acm.2025.153814

the ELANE gene. SCN is characterized by severe neutropenia with recurrent infections, and some patients with SCN may also have oral manifestations. We reported a 30-year-old woman with recurrent mouth ulcers and severe chronic periodontitis. Whole-exome sequencing analysis revealed that it was a novel missense mutation on ELANE (c.377C > T (p. Ser126Leu)). Although the patient's absolute neutrophil value fluctuated around $0.2 \times 10^9/L$ all year round, the patient rarely developed severe infection after the age of 18 years, so the patient refused G-CSF treatment and asked for long-term outpatient follow-up. This study summarized and analyzed this case with the aim of improving clinicians' understanding of severe congenital neutropenia with periodontal lesions as the main clinical manifestation.

Keywords

ELANE, Congenital Neutropenia, Periodontal Inflammation, Oral Ulcer

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1. 病例报告

先天性中性粒细胞减少症(CN)是一种由基因突变引起的罕见的血液病,其遗传模式包括常染色体隐性遗传、常染色体显性遗传和 X 连锁形式[1] [2]。CN 的特征是持续的中性粒细胞绝对计数(ANC)下降($<1.5 \times 10^9/L$)合并反复感染,一些患者还可能口腔表现。其中,重度先天性中性粒细胞减少症(Severe Congenital Neutropenia, SCN)的 ANC 可小于 $0.5 \times 10^9/L$ [3] [4]。因为 SCN 可以进展为急性髓系白血病(CN/AML),所以也有人称之为白血病前期骨髓衰竭综合征[5]。因此,在临床上早期发现及早期治疗对于 SCN 患者的预后至关重要。不同基因突变类型所导致的 SCN 在临床表现上也有所不同。本文通过报道 1 例以牙周病变为主要临床表现的 ELANE 上新型突变的患者,以期提高对该病的认识,为临床诊断提供一定参考。

患者,女,30岁,因“发现白细胞减少5年”入院。患者自诉2周岁时因水痘住院后频繁出现口腔溃疡、发热,经对症治疗后好转。患者18周岁后发热频率明显减低,但仍然反复发作口腔溃疡。6年前因公司体检“首次”发现白细胞减少,血常规提示 WBC $2.0 \times 10^9/L$,中性粒细胞绝对值(ANC) $0.2 \times 10^9/L$,HGB、PLT 正常;患者未予重视。半年前,患者来我院复诊中性粒细胞减少。

查体:全口牙龈红肿,后牙松动。体表未见淋巴结肿大。心、肺、腹未见异常。无脊柱畸形,关节无肿痛,四肢肌力、肌张力可。脑膜刺激征阴性。生理反射存在,病理反射未引出。

检验检查:血常规:WBC $3.49 \times 10^9/L$,ANC $0.04 \times 10^9/L$,HGB 123 g/L,PLT $241 \times 10^9/L$ 。血 PNH (CD55/CD59) + FLAER (外周血)未检出 PNH 克隆细胞;抗 ANCA、ENA 谱、类风湿四项等常见自身抗体均阴性。双侧颈部、锁骨上、腋窝及腹股沟淋巴结提示未见明显异常。腹膜后超声未见明显肿块,肝胆胰脾超声未见明显异常。骨髓流式细胞学免疫分型显示 CD34 + CD117 + 原始细胞比例稍高,表型未见明显异常;粒系比例减低,发育模式异常;单核细胞比例增高,以成熟阶段为主。骨髓细胞学提示:粒红系细胞少见。染色体核型:46,XX。

全外显子组测序:发现 ELANE 基因错义突变(c.377C > T) (exon4) (p. S126L);患者父亲及母亲均无该基因位点变异(图 1)。该位点是我国首例在先天性粒细胞减少症中发现的新的变异位点。患者最终诊断为 ELANE 相关的重度先天性中性粒细胞减少症。

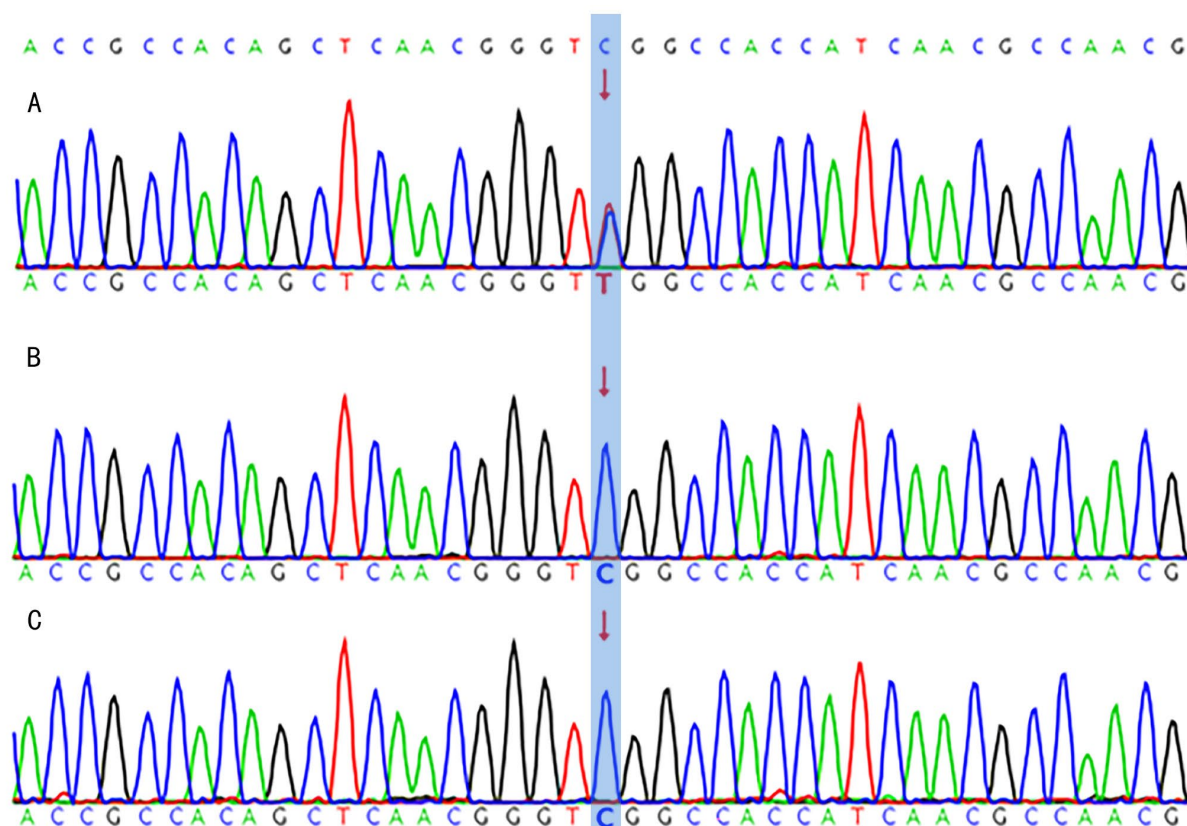


Figure 1. The results of ELANE gene sequencing of the patient and his parents: (A) The patient had c.377C > T locus variants; ((B) (C)) The father and mother of this patient who did not have c.377C > T locus variants (the arrow is the pathogenic variant locus)

图 1. 患者及其父母的 ELANE 基因测序结果: (A) 本例患者存在 c.377C > T 位点变异; ((B) (C)) 本例患者的父亲及母亲均无 c.377C > T 位点变异(箭头处为致病变异位点)

2. 讨论

先天性中性粒细胞减少症(Congenital Neutropenia, CN)在临床上通常表现为反复细菌感染及口腔病变,但有一些罕见的基因突变,比如 JAGN1,也可引起全身多器官多系统的累及,表现为如身材矮小、抽搐、骨骼异常、幽门狭窄、胰腺功能不全等[6] [7]。我们所报道的这例患者从 2 岁起便有反复的口腔溃疡(25 周岁时合并有慢性牙周炎)、发热(18 周岁后鲜有),据患者及其父母回忆他们均未注意到患者幼时的中性粒细胞异常,直到患者 24 周岁于单位体检中才第一次注意到中性粒细胞的严重减少,此后患者规律复查血常规,中性粒细胞绝对值计数常年处于 $0.2 \pm 0.1 \times 10^9/L$ 左右。这里需要与周期性粒细胞减少症(Cyclic Neutropenia, CyN)作鉴别, CyN 的典型临床表现包括发热、口腔溃疡、淋巴结肿大、严重感染等,常见的致病基因也包括 ELANE 基因,也就是说周期性粒细胞减少症同样可以引起中性粒细胞的减少及口腔病变,但中性粒细胞减少通常是以 21 ± 3 天为周期的[8]-[10],由患者提供的中性粒细胞动态检测数据提示该患者的中性粒细胞减少并不具有周期性。CN 与 HAX1、ELANE、G6PC3 等多种基因突变相关,最常见的是 ELANE 中的常染色体显性基因突变,约见于 50%~60%的 SCN 患者[11] [12]。ELANE 基因编码中性粒细胞弹性蛋白酶,这是一种在骨髓单核细胞及其前体中表达的丝氨酸蛋白酶,当 ELANE 基因突变时,其表达的错误折叠蛋白酶的积累,一方面可激活死亡信号引发未成熟中性粒细胞凋亡,另一方面也可阻碍未成熟中性粒细胞进一步分化及发育,导致中性粒细胞减少症[13] [14]。我们通过基因检测发现

患者本人的 ELANE 基因错义突变(c.377C > T) (exon4) (p. S126L), 但患者的父母接受检测后并未发现同种基因突变。结合患者 2 周岁起频发口腔溃疡, 血常规提示中性粒细胞绝对计数常年低于 $0.5 \times 10^9/L$ 且并不具有周期性变化, 最终诊断为 SCN。

SCN 的传统治疗是通过应用粒细胞集落刺激因子来实现安全的中性粒细胞计数, 可以显著增加 SCN 患者的中性粒细胞计数并改善牙周状态[15]。尽管如此, 仍有 10% 的患者患有 G-CSF 难治性中性粒细胞减少症, 他们需要接受造血干细胞移植[16] [17]。对这类患者来说, 造血干细胞移植可能是唯一有效的彻底治愈手段。此外, Nasri 等人在 2024 年首次提出使用黄吡啶醇治疗 CN 的可能[18], 也有研究表明, 治疗性基因编辑也有望成为除造血干细胞移植外彻底治愈 SCN 的手段[19] [20]。由于本例患者目前主要的临床表现为口腔相关病变, 且成年后少有发热或除口腔相关病变以外的其他严重感染, 因此, 患者拒绝常规使用 G-CSF 治疗, 我们反复向患者交代相关风险, 患者仍拒绝 G-CSF 治疗, 但患者同意规律复查血常规, 血液科门诊随访, 我们也向患者进行了健康宣教。

SCN 虽为遗传病, 但在本例患者中并未发现其父母有相同的基因突变位点, 在 2023 年也同样报道过一例父母及哥哥均无相同基因位点的先天性中性粒细胞减少症患者, 因此, 有关 SCN 的遗传机制仍然需要进一步探讨。患者中性粒细胞绝对计数常年低于 $0.5 \times 10^9/L$, 且 SCN 有转变为急性髓系白血病和骨髓增生异常综合征的风险[21] [22], 其临床结局不容乐观, 因此长期随访以及发生感染时及时的处理至关重要。

声 明

该病例报道已获得病人的知情同意。

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