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一例少见青少年 T 幼淋巴细胞白血病的病例报道及文献回顾 *

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摘要 目的:报道一例少见幼年淋巴细胞白血病(T-PLL)患者的病例资料及诊疗过程,并通过文献复习总结了 T-PLL 的临床特点和诊疗措施。**方法:**对病例资料进行对比分析,同时通过文献回顾研究 T-PLL 的特点及发生、发展及诊疗情况。**结果:**本病例为少见青少年型幼淋巴细胞白血病,细胞以成熟小淋巴细胞为主,特征免疫表型为 CD7⁺CD5⁺CD4⁺CD8⁺CD3⁺,无染色体异常,有 TCR 基因重排。**结论:**T-PLL 病例具有多态性及复杂性,在临床诊断中需要密切联系临床特点及实验室诊断,综合判断疾病情况,做出最优治疗方案。

关键词:幼淋巴细胞白血病(T-PLL);免疫表型;临床特点及实验室诊断

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Diagnosis and Treatment of a Rare Adolescent T-cell Prolymphocytic Leukemia and Literature Review*

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ABSTRACT Objective: To report a rare type of adolescent of T-cell Prolymphocytic Leukemia (T-PLL), and summarize the clinical features and diagnostic measures of T-PLL through reviewing the literatures. **Methods:** The clinical data of a rare type of adolescent of T-PLL was analyzed. The characteristics, occurrence, development and diagnosis and treatment of T-PLL were studied through literature review. **Results:** This case is a rare juvenile lymphoblastic leukemia. Most of the cells are mature small lymphocyte. The characteristic immunophenotype is CD7⁺CD5⁺CD4⁺CD8⁺CD3⁺. There is no chromosomal abnormality and TCR gene rearrangement positive. **Conclusions:** T-PLL has the characteristics of polymorphism and complexity. The clinical characteristics and laboratory diagnosis should be closely linked in clinical diagnosis, and disease conditions should be judged comprehensively to make the best treatment plan.

Key words: T-cell Prolymphocytic Leukemia (T-PLL); Immune phenotype; Clinical characteristics and laboratory diagnosis

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前言

T 幼淋巴细胞白血病(T-PLL)是一种少见类型的淋巴细胞白血病,属于胸腺后 T 淋巴细胞肿瘤^[1],只占成熟淋巴细胞白血病的 2%^[2-4],欧美发病较多,国内少见。T-PLL 具有独特的细胞形态、免疫表型、细胞遗传学及分子生物学特征^[5],以外周血异常淋巴细胞比例增高、病情进展迅速、侵袭性强、全身肝脾淋巴结多发肿大、对化疗药物不敏感、生存期短^[6,7],部分病例有皮肤损害、浆膜腔积液及神经系统损害为主要特点^[8,9]。T-PLL 30 岁以上发病^[10],老年人为主,平均年龄为 65 岁^[11,12],青少年少见。本病不同病例临床症状及实验室检查存在异质性,从而导致疾病的诊断及鉴别诊断相对困难,临床治疗方案的选择不尽相

同。本病的本质还需要进一步探究,选择合适的临床及实验室指征,为治疗提供帮助^[13]。本病在报道中以中老年人为主,属于成熟淋巴细胞增殖性疾病,罕见发生于青少年^[12]。本文将报道一例 13 岁的 T-PLL 患者的诊疗过程,通过文献回顾,比较青少年型 T-PLL 和中老年型的异同点。

1 资料与方法

1.1 病例资料

患者,男,13 岁,2017 年五月上旬无明显诱因出现发热,体温最高 38℃,无寒战畏冷,无咳嗽咳痰。5 月 7 日就诊于当地三甲医院,给予消炎治疗后体温下降,但维持不佳,停药后反复,且随后出现腹痛,无腹泻,血常规示:白细胞计数 $4.2 \times 10^9/L$;血

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红蛋白 126 g/L;血小板计数 $147 \times 10^9/L$,腹部 B 超示:颈部、肠系膜多发淋巴结肿大,肝脾轻度肿大,乳酸脱氢酶 275IU/L,肝肾功能正常,外周血涂片淋巴细胞占 96%。5 月 18 日复查血常规:白细胞计数 $93.89 \times 10^9/L$;淋巴细胞比例 76.7%。给予抗感染、激素治疗,患者体温正常,淋巴结缩小,腹痛消失,为进一步治疗于 5 月 22 日入住我院,血常规示:白细胞 $35.45 \times 10^9/L$,血红蛋白 122 g/L,血小板计数 $221 \times 10^9/L$,行实验室检查。

1.2 细胞形态学及免疫

髂后上棘穿刺抽取骨髓液制作骨髓涂片用于形态学、免疫学检测,同时采左手无名指末梢血制备血片,骨髓片分类 250 个有核细胞,血片分类 100 个有核细胞(有核红细胞除外),免疫表型检测抗体为 CD4、CD8、CD3、TCR、CD34、CD33、CD13、CD117、HLA-DR、cCD3、cCD79a、cMPO、CD7、CD2、CD56、CD19、TDT,流式细胞仪及相关检测抗体均购自美国贝克曼库尔特公司,细胞膜抗体表达以大于 20% 为阳性表达,膜内抗体表达以大于 10% 为阳性表达,"c" 代表细胞内。

1.3 荧光原位杂交技术(FISH)分析

取骨髓液清洗两遍,弃上清,加 KCL 水浴 20 min,加冰醋酸 2 mL 固定、制片,干燥后加荧光探针,探针为购自广州安必平医药科技股份有限公司的白血病相关基因检测试剂盒,用购自美国 ThermoBrite 公司的荧光原位杂交仪杂交,荧光显微镜阅片,计数 200 个细胞,阳性细胞大于 4% 为阳性。

1.4 RT-PCR 及二代测序

取乙二胺四乙酸二钾(EDTA-2K)抗凝剂的骨髓液,抽提 RNA,用白血病相关融合基因检测试剂盒进行逆转录及扩增,

以上试剂均购自上海睿昂生物技术公司,PCR 仪购自美国安捷伦公司。结果判断以扩增 20 个循环起跳为阳性;测序仪购自美国 ABI 公司。

2 结果

骨髓片形态学特点:成熟淋巴细胞 75.6%,幼淋巴细胞占 6.4%,成熟淋巴细胞形态规则,核染色质聚集,核质比高,未见核仁,幼淋巴细胞形态规则,核染色质聚集,可见大而圆的 2-3 个核仁,化学染色髓过氧化物酶(POX)阴性,糖原(PAS)散在阳性。外周血片幼淋巴细胞占 14%(图 A),细胞胞体小、形态规则染色质聚集浓染。骨髓活检显示满片成熟规则小淋巴细胞(图 B)。免疫分型结果为 $CD7^+CD5^+CD4^+CD8^+CD3^+$,其他检测抗体均阴性。FISH 探针检测 14q11-q32、inv(14)(q11;q32)、inv(14)(q11;q32)、8q 三体均阴性。PCR 检测出 TCR 基因重排(图 C),根据 WHO 标准,确诊为 T-PLL。由于患者精神佳,皮肤黏膜未见出血点,对症治疗后,患者出院,未进行特殊治疗,至六月底复查血常规白细胞波动在 $35.45-50.6 \times 10^9/L$ 。7 月 1 日白细胞为 $19.32 \times 10^9/L$,7 月 4 日白细胞为 $17.84 \times 10^9/L$,8 月 23 日,患者再次入院,患者一般状况良好,无特殊不适,白细胞计数 $9.85 \times 10^9/L$,血小板计数 $203 \times 10^9/L$,血红蛋白 119 g/L。虽然未行特殊治疗肿大淋巴结缩小,外周血白细胞明显减低,但外周血淋巴细胞比例一直维持在 90% 以上,为控制病情,给予 COP 方案化疗,具体环磷酰胺 0.6g d1;长春新碱 1 mg d1;地塞米松 8 mg d1-5,COP 化疗顺利,无恶性呕吐,未诉特殊不适,后续按照计划复查,用药,随访一直良好。

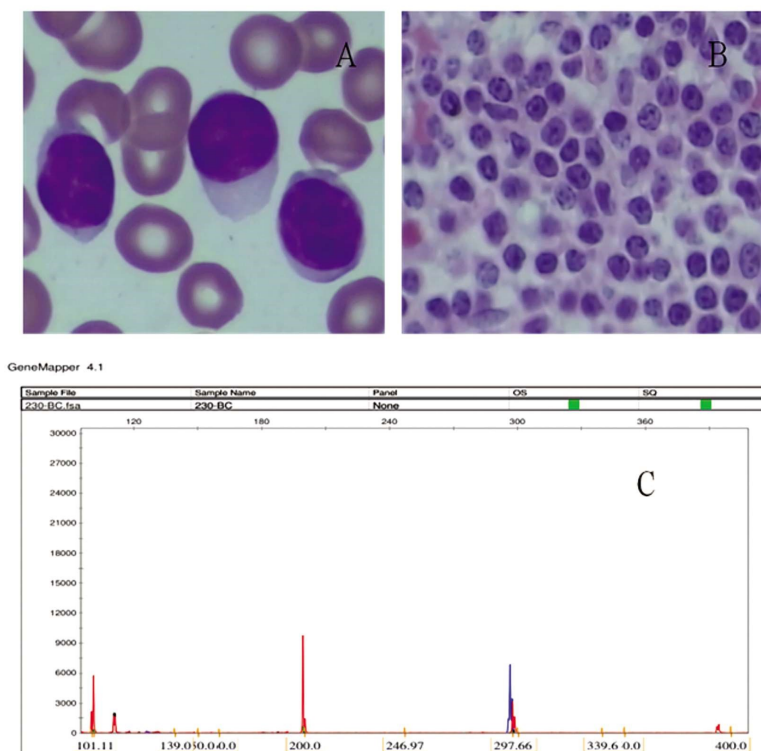


图 1 骨髓涂片、骨髓活检细胞形态及 TCR 基因测序图谱图

Fig.1 Bone marrow smear, bone marrow biopsy cell morphology and TCR gene sequencing map

注:A 为外周血小淋巴细胞,染色质聚集、浓染。B 为骨髓活检,形态规则的小淋巴细胞。C 为 TCR 基因 BC(Dβ-Jβ)297.66 片段重排。
Note: Fig. A is a small lymphocyte in peripheral blood. Chromatin is aggregated and strongly stained. Fig. B is a small lymphocyte with regular morphology in bone marrow biopsy. Fig. C is a rearrangement of BC (Dβ-Jβ) 297.66 fragment of TCR gene.

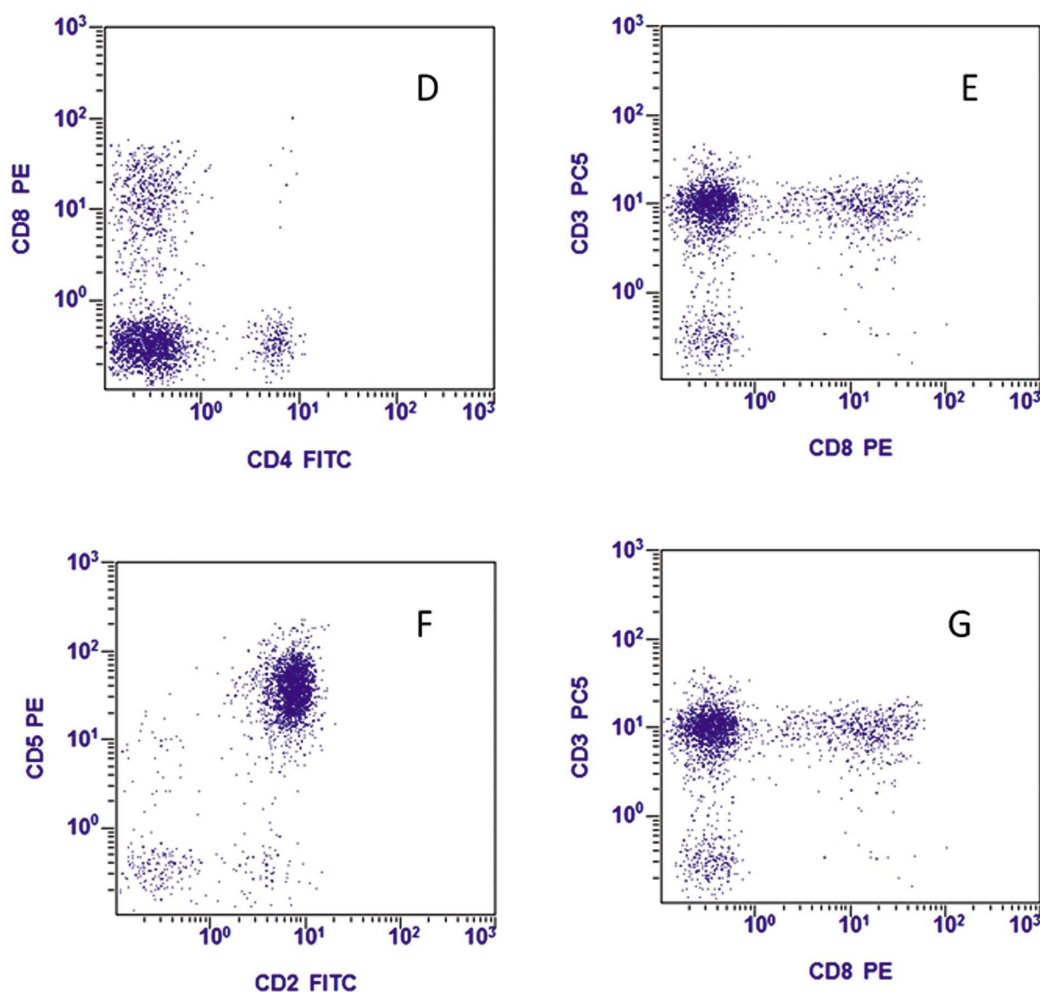


图2 流式细胞术免疫分型散点图

Fig.2 Flow cytometry scatter plot of immunophenotyping

注:D为抗体CD4/CD8双参数散点图。E为抗体CD3/CD8双参数散点图。F为抗体CD2/CD5双参数散点图, G为为抗体CD3/CD8双参数散点图。

Note: Fig. D is a two-parameter scatter plot of antibody CD4/CD8. Fig. E is a two-parameter scatter plot of antibody CD3/CD8. Fig.F is double-parameter scatter plot of antibody CD2/CD5 and Fig.G is double-parameter scatter plot of antibody CD3/CD8.

3 讨论

T-PLL是一种少见类型的主要发生在成人的淋巴细胞白血病,病情发展迅速,患者肝脾淋巴结肿大,外周血淋巴细胞比例增高,部分患者伴有皮肤或精神损害,病程一年左右^[6,14-15]。幼稚淋巴细胞呈中等大小,胞核规则或不规则,核染色质浓集,具有明显核仁,胞质可见一些强嗜碱性突起^[16]。但也有一小部分病例外周血以成熟小淋巴细胞为主,只有电子显微镜可见的核仁,核染色质聚集粗糙,肿瘤细胞相对温和,病情发展缓慢,对化疗药物敏感,这些病例最早被称为T-CLL(慢性T淋巴细胞白血病)。直到2008年,WHO将典型T-PLL和T-CLL合并,统称为T-PLL^[17,18],因为大多数病例两者有着相同的临床表现及基因表型,相似的治疗手段,共同的耐药特点和短暂的生存期,但一直以来的争论并没有减少^[19,20],各个学者的观点也不尽相同,有报道认为应该恢复T-CLL^[21],因为T-CLL属于小淋巴细胞惰性肿瘤,病情发展缓慢,对化疗药物敏感,生存期长,如果按照T-PLL进行大剂量化疗,会导致过度治疗,减少生存质量

和生存期。Samuel Adediran, MD等^[22]报道了一例78岁的T-PLL患者,最初外周血及骨髓淋巴细胞为成熟小细胞,染色质聚集浓缩,未见核仁,全身未见淋巴结肿大,也没有肝脾肿大,免疫分型为CD3(+)CD4(+)CD5(+)CD8(-),染色体核型为45,X,-Y^[18],XY^[2],在确诊后7年内没有任何症状,也没有进行治疗,18年后才出现肝脾淋巴结肿大,严重腹水,外周血高白细胞,给予一个疗程阿珠仑单抗治疗,肝脾淋巴结缩小,白细胞基本恢复正常,但腹水没有改善,患者健康状况不佳,最后死亡。但也有报道持不同意见,认为应该保持WHO分型的T-PLL和T-PLL-SV^[23](小细胞性T-PLL),因为T-PLL-SV的独特特性并不绝对,有些被认为是发生在儿童的惰性肿瘤,结果发展很迅速,浸润性强,对化疗药物不敏感,预后差,生存期短^[6]。T-PLL也可能有T-PLL-SV的特点,T-PLL是侵袭性的,但也有明显核仁的T-PLL是进展缓慢的,呈惰性特点,也有些病例等到确诊以后已经过了惰性期,而呈现浸润发展,所以WHO的T-PLL和T-PLL-SV的分型方法是适当的^[23]。部分文献认为疾病的惰性状态只是前期状态,等发展为急进状态和典型T-PLL的疾病

特点、生存期没有差异^[24]。由于 T-PLL 病例少,缺少系统性研究,以往报道中主要是个案分析,而且基本都是发生在三十岁以上的成年人^[25]。查阅近年国内外文献,我们发现只有 Bryan Mitton 等^[11]报道了一例 16 岁的青少年病例,此患者伴随脊柱侧弯,存在神经系统症状,化疗无法耐受,最后干细胞移植。我们报道的是一例 13 岁男性病例,这是我们查询到文献报道 T-PLL 最小年龄,以成熟的小细胞为主,胞体规则,核染色质粗糙、聚集,免疫分型为 CD5⁺CD4⁺CD8⁺CD3⁺CD7,大多数情况下,T-PLL 大部分 CD2、CD3、CD7、CD45 阳性^[26,27],CD4⁺/CD8⁻^[28,29],CD4⁺/CD8⁺ 只发生在少数病例^[30,31],检出 TCR 异常基因重排,淋巴结及肝脾轻度增大,临床症状轻,在未采取化疗情况下,外周血淋巴细胞进行性减低,最后到恢复到正常范围,这可能是细胞恶性程度较低,部分对抗生素也敏感,为了防止肝脾淋巴结进一步扩大而开始 COP 方案化疗,一个疗程后缓解,患者精神佳,后续按照计划复查,用药,随访一直良好。

总之,T-PLL 是一种少见病例,发生于青少年的病例更少,还需要更多临床资料进一步研究^[24]。目前,根据形态学、免疫学等方法很难确定肿瘤为惰性还是侵袭性,如果是惰性大剂量化疗会过度治疗从而进一步减少患者生存质量,如果为侵袭性的而选择消极化疗,会延误病人病情,尤其青少年,对药物耐受性差,病情发展迅速,需要准确判断疾病的性质,以提供最恰当的治疗方案。以后的研究可以在分子生物学和染色体方面寻找与疾病的相关特性。这方面已经有些报道,但还需要时间验证和扩大范围研究。

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(上接第 3852 页)

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