

• 病例报告 •

慢性 NK 细胞增殖性疾病 1 例并文献复习*

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[关键词] 慢性 NK 细胞增殖性疾病;大颗粒淋巴细胞;自然杀伤细胞

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A case report of chronic lymphoproliferative disorders
of natural killer cells and literature review

Summary The phenomenon of persistent natural killer (NK) cell lymphocytosis has been recognized as the provisional diagnostic entity 'chronic lymphoproliferative disorder of natural killer cells' (CLPD-NK) in the WHO classification of hematopoietic tumors. However, disease recognition is problematic because NK cells lack a uniquely rearranged antigen receptor gene (such as T-cell receptor) to serve as a marker of clonal cellular expansion and to facilitate distinction from reactive processes. The paucity of literature suggests that CLPD-NK is rare. Here we report a case of CLPD-NK and discuss it with the relevant literatures.

Key words chronic lymphoproliferative disorders of natural killer cell; large granular lymphocyte; natural killer cell

慢性 NK 细胞增殖性疾病是起源于成熟 NK 细胞系的恶性淋巴细胞增殖性疾病,作为 2008 年 WHO 关于淋巴造血组织肿瘤分类中的独立类型,其发病率极低。我们诊治慢性 NK 细胞增多症(CNKL) 1 例,将其临床资料报告如下,并结合文献进行讨论。

1 病例资料

患者,女,64 岁,因“间断乏力、气短 1 个月”就诊于我院。患者 1 个月前无明显诱因出现乏力、气短,于航空医院查血常规示:WBC $30.64 \times 10^9/L$, HGB 129 g/L, RBC $4.54 \times 10^{12}/L$, PLT $231 \times 10^9/L$, LYMPH $27.50 \times 10^9/L$ 。给予抗感染治疗,白细胞略有下降,就诊于我院门诊,查血常规示:WBC $21.27 \times 10^9/L$, HGB 140 g/L, RBC $4.81 \times 10^{12}/L$, PLT $205 \times 10^9/L$, LYMPH $17.61 \times 10^9/L$ 。骨髓形态学示:幼稚淋巴细胞占 0.5%,成熟淋巴细胞占 33.5%,外周血成熟淋巴细胞占 81%。骨髓活检示:骨髓增生明显活跃,脂肪组织减少,粒细胞增生活跃,各阶段均可见,红系增生活跃,可见幼红细胞簇,巨核细胞不少,淋巴细胞比例增高。门诊遂以“淋巴细胞增高待查”收住院。2011 年曾因胆囊结石行胆囊切除术,当时血常规示:WBC $12.79 \times 10^9/L$, HGB 119 g/L, RBC $3.60 \times 10^{12}/L$, PLT $171 \times 10^9/L$, LYMPH $1.06 \times 10^9/L$ 。个人史无异

常。父母均患食管癌已去世。体检:浅表淋巴结未触及,胸骨无压痛,心肺未见异常,肝脾无肿大。入院后完善检查,血常规示:WBC $20.45 \times 10^9/L$, HGB 131 g/L, RBC $4.56 \times 10^{12}/L$, PLT $170 \times 10^9/L$, LYMPH $18.52 \times 10^9/L$, RET $49.70 \times 10^9/L$ 。肿瘤标志物、自身抗体谱、心肌酶谱、肝肾功能、血电解质、结核相关检查、HCMV、EBV、血沉、肝炎病毒、血脂、血清蛋白电泳、免疫球蛋白系列、Coomb's 试验、心电图、腹部 B 超均阴性。胸部 CT 示:右肺中上叶局限性肺气肿。染色体:46,XX。免疫原位杂交:P53(17p13)、13q14、12 号染色体、11q22 位点均未见明显异常。外周血成熟淋巴细胞占 86%。符合慢性淋巴细胞白血病(图 1a、b)。骨髓形态学:骨髓增生明显活跃,粒系占 32%,红系占 15.5%,粒系增生减低,形态大致正常;红系增生活跃偏低,成熟红细胞大致正常;成熟淋巴细胞占 51.5%,巨核系 111 个,血小板易见(图 1c、d)。骨髓活检示:淋巴细胞比例增高,部分区域可见成片小淋巴细胞(图 1e、f)。骨髓细胞免疫分型:异常细胞占 60.47%,表达 CD7, CD11B, HLA-DR, CD16, CD56, CD38, CD2, CD11C, cCD3,考虑 NK 细胞免疫表型(图 2)。

2 讨论

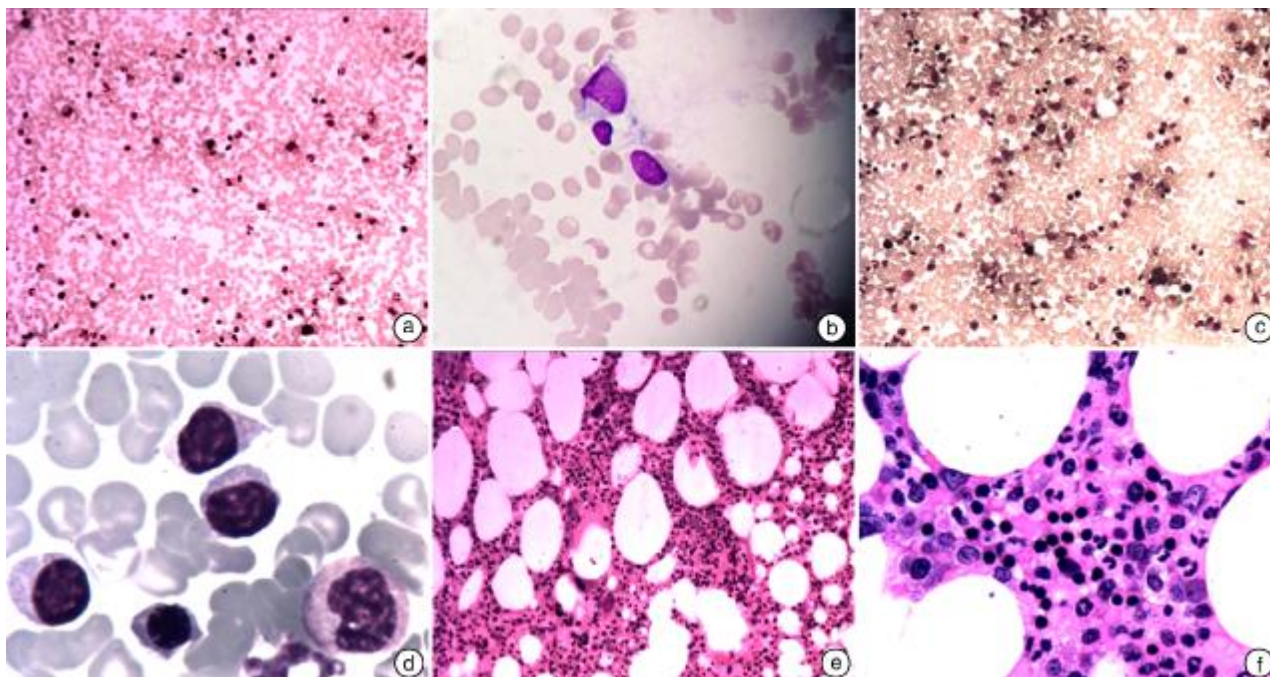
1975 年 Brouet 等^[1]首次描述了一类 T 细胞来源的慢性淋巴细胞白血病,随后于 1985 年由 Loughran 等^[2]命名为大颗粒淋巴细胞白血病,该命名在 1999 年被 WHO 淋巴与造血组织肿瘤分类中采用^[3]。大颗粒淋巴细胞白血病起源于成熟 T

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a:外周血涂片(×100);b:外周血涂片(×1000);c:骨髓细胞涂片(×100);d:骨髓细胞涂片(×1000);e:骨髓活检(×100);f:骨髓活检(×1000)。

图1 细胞学及病理学检查

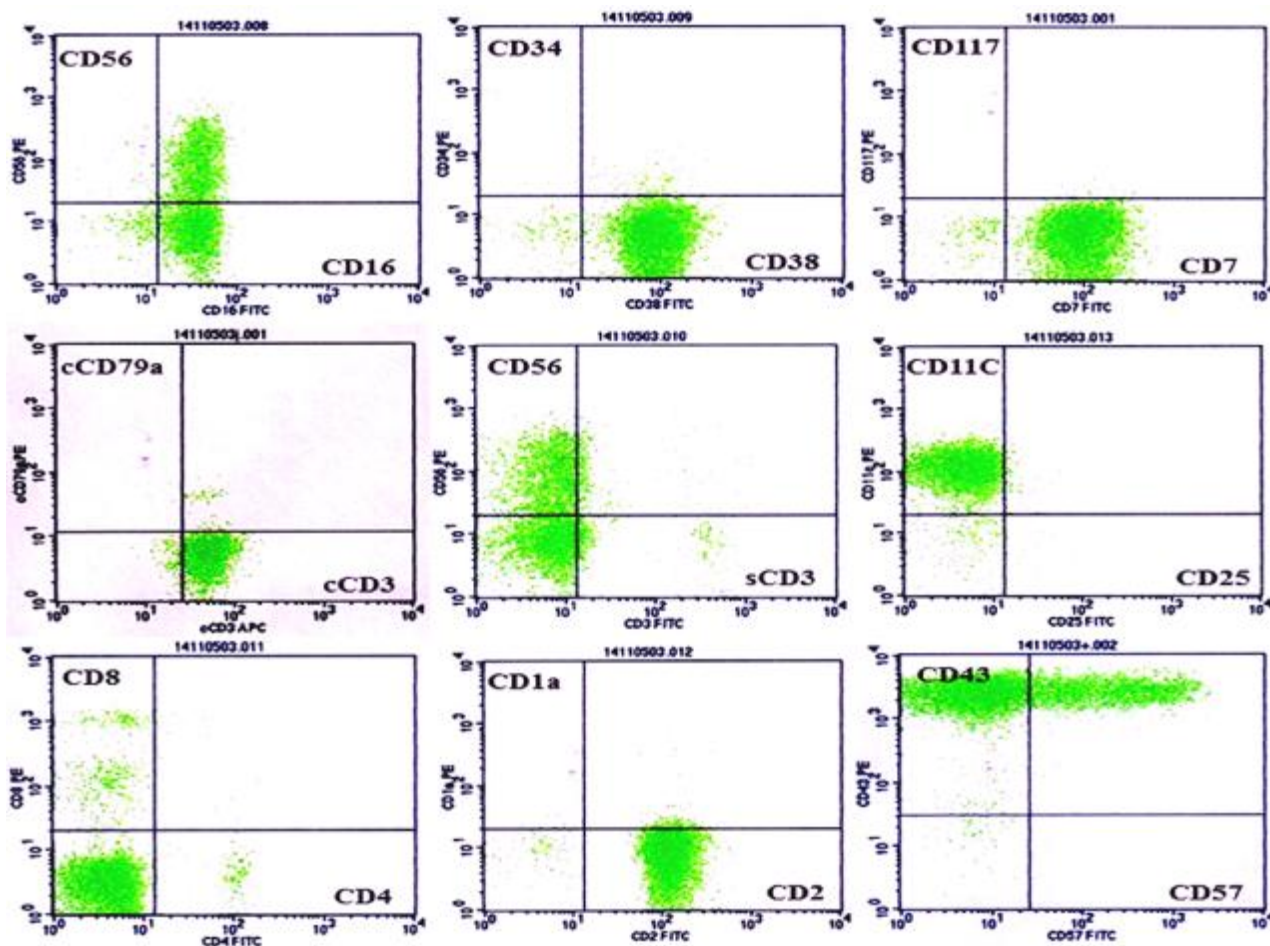


图2 骨髓细胞表型分析

细胞系或成熟 NK 细胞系,因成熟 NK 细胞来源的大颗粒淋巴细胞白血病发病率极低,长期并未得到重视,也未与 T 细胞性大颗粒淋巴细胞白血病分开研究。

CNKL 由 Tefferi 等^[4]在 1994 年首次提出,被认为是一种罕见的起源于成熟 NK 细胞的淋巴增殖性疾病,约占所有大颗粒淋巴细胞白血病的 5%。2008 年 WHO 造血和淋巴组织肿瘤分类方案正式将 CNKL 作为一个独立的病种列入成熟 T/NK 细胞淋巴瘤的范畴^[5],但 CNKL 的临床表现更接近 T 细胞性大颗粒淋巴细胞白血病^[6-7],而与其他来源于 NK 细胞的肿瘤具有明显不同的临床过程。

目前关于 CNKL 诊断的争议仍较多,主要问题是本病与反应性 NK 细胞增多鉴别困难。2008 年 WHO 淋巴造血组织肿瘤分类中 CNKL 的诊断标准为:①外周血 NK 细胞绝对值 $\geq 2 \times 10^9/L$;②持续 6 个月以上;③排除诊断明确的继发性疾病。迄今为止尚难以确认 CNKL 中 NK 细胞的克隆性,CNKL 的恶性起源尚不明确,临床上排除继发性疾病仍比较困难。

外周血 NK 细胞增多与多种血液系统疾病及非血液系统疾病均密切相关,可见于多种疾病,如免疫性血小板减少性紫癜、骨髓增生异常综合征、非霍奇金淋巴瘤、实体肿瘤、皮肤病及神经系统疾病等^[8]。最近 Kim 等^[9]研究发现,慢性粒细胞白血病在给予达沙替尼治疗后会导导致 NK 细胞的增多,患者 NK 细胞的功能是正常或增强的,NK 细胞增多者也取得了更好的细胞遗传学及分子生物学缓解。在缺乏特异性克隆标志的前提下,临床特征在鉴别反应性 NK 细胞增多和 CNKL 时显得尤为重要,在有可能导致 NK 细胞增高疾病时,诊断为 CNKL 就需要非常谨慎。

如何寻求更特异性 CNKL 的克隆性证据是在疾病研究中最迫切的问题。Zambello 等^[10]发现 CNKL 患者异常表达 NK 细胞免疫球蛋白样受体(KIRs),CD94/NKG2A 型多见,并且多表现为活化性的 KIRs。KIRs 的限制性表达可能作为 CNKL 的克隆性证据,但仍需要更多的研究支持。Jerez 等^[11]发现 STAT3 基因突变可见于 30% 的 CNKL 患者,基因突变也参与了疾病的进程,并且似乎预示更差的临床过程。STAT3 的突变并未见于缺铁性贫血及 NK 细胞反应性增高患者,提示其可作为鉴别 CNKL 与反应性 NK 细胞增高的检查。

Yeh 等^[12]研究发现 NK 细胞的功能是有缺陷的,细胞毒性测定发现 CNKL 患者 NK 细胞功能缺陷,其分泌的细胞因子也较正常人减少。Balsamo 等^[13]发现 CNKL 患者来源的 NK 细胞不能与单核细胞来源的 DC 细胞相互作用,从而打破了两者的平衡,并促进了 NK 细胞的慢性增殖。NK 细胞功

能的缺陷也从另一个方面证实了 CNKL 是具有与反应性 NK 细胞增多完全不同的疾病。

流式细胞术是诊断 CNKL 必不可少的手段,其一般表达 CD2,CD7 及 CD16,一般不表达 CD3,CD4 及 CD5,CD56 则无特异性,可有不同程度的表达,这也是与正常 NK 细胞免疫表型明显不同之处^[14]。在本研究中患者为中老年女性,NK 细胞持续增多长于 6 个月,NK 细胞表型符合典型 CNKL 改变,无明确导致 NK 细胞增多的基础疾病,且疾病发展非常缓慢。虽然未找到克隆性证据,但综合疾病的临床表现,仍可诊断为 CNKL。

CNKL 呈现惰性临床过程,预后良好,少数患者出现血细胞减少、皮肤脉管炎、周围神经病变和脾脏肿大,急性肾小球肾炎等,该病也可能进展为侵袭性 NK 细胞白血病^[15]。本例患者随访 1 年,未给予特殊干预措施,疾病也未见进展,提示其惰性的临床过程,但随访时间较短,我们仍将持续关注该患者的转归。

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继发于乳腺癌的治疗相关性伴 t(9;11)(p22;q23); (MLLT3-MLL) 急性单核细胞白血病 1 例并文献复习*

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[关键词] 乳腺癌; 治疗相关性白血病; 急性单核细胞白血病; t(9;11)(p22;q23)急性髓细胞白血病; MLLT3-MLL 融合基因

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A case of the t(9;11)(p22;q23); (MLLT3-MLL) breast cancer treatment-related acute monocytic leukemia and literature review

Summary To explore clinical features, diagnosis and treatment of solid tumor treatment-related acute monocytic leukemia (M_5) with 11q23, we analyzed a case of the breast cancer treatment-related M_5 with t(9;11)(p22;q23); (MLLT3-MLL), and carried on the literature review. The patient was treated with 6 cycles of chemotherapy of TEC regimens one year ago. She was admitted with acute leukemia, the myeloproliferation was extremely active, with immature monocytes and mature monocytes accounting for 62% and 31%, respectively. Karyotype analysis was 46, XX, t(9;11)(p22;q23)[20], and MLLT3-MLL was positive. According to classification rules of WHO 2008 hematopoietic system disease, she was diagnosed as AML with t(9;11)(p22;q23) abnormality. Because of the patient with a preliminary history of breast cancer chemotherapy, 11q23 MLL gene rearrangement could be found in a shorter incubation period of treatment-related leukemia, so the patient was diagnosed as treatment-related M_5 with 11q23/MLL. The breast cancer treatment-related M_5 with t(9;11)(p22;q23); (MLLT3-MLL) is clinically rare, 11q23 MLL gene rearrangement suggest that patients belong to a shorter incubation period of treatment-related leukemia, the prognosis is poor. We should strengthen the understanding of this disease.

Key words breast cancer; treatment-related leukemia; acute monocytic leukemia; t(9;11)(p22;q23) acute myeloid leukemia; MLLT3-MLL fusion gene

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