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乳腺恶性血液病的病理类型、临床特点及生存分析*

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摘要 目的:探讨乳腺恶性血液病的病理分型、患者的临床特征及预后。**方法:**回顾性分析 2014 年 1 月至 2019 年 1 月空军军医大学西京医院收治的 33 例乳腺恶性血液病患者的病理分型、临床特征及预后。**结果:**33 例患者中,32 例为女性,1 例为男性,平均年龄为 45.5 岁(12-78 岁)。经病理确诊 29 例(29/33, 87.9%)为非霍奇金淋巴瘤,其中弥漫大 B 细胞淋巴瘤(18/29, 62.1%)最为常见,其次是 NK/T 细胞淋巴瘤(3/29, 10.3%),B 淋巴母细胞白血病/淋巴瘤(2/29, 6.8%),而伯基特淋巴瘤、滤泡淋巴瘤、原发皮肤间变大细胞淋巴瘤各 1 例(1/29, 3.4%),其余 3 例未进一步分型。此外,1 例(1/33, 3.0%)霍奇金淋巴瘤,3 例(3/33, 9.1%)急性白血病复发累及乳腺。原发性乳腺恶性血液病为 19 例(57.6%),继发性为 14 例(42.4%),病变主要累及右侧乳腺(18 例, 54.5%),其次为左侧(10 例, 30.3%),双侧均累及的为少数(5 例, 15.2%)。19 例原发性乳腺恶性血液病均为淋巴瘤,与 14 例继发性乳腺恶性血液病相比,其血小板计数明显升高($P=0.004$), $\beta 2$ -MG 显著降低($P=0.049$),B 症状少($P=0.017$),Ann Arbor 分期主要为 I-II 期($P<0.01$),骨髓受累少($P<0.01$)等特点。生存分析提示原发性乳腺恶性血液病患者比继发性患者生存期更长($HR=9.846, P=0.002$)。恶性血液病累及骨髓可导致生存期显著缩短($HR=6.434, P<0.01$)。**结论:**乳腺恶性血液病患者以中年女性为主,原发性乳腺恶性血液病比继发性发病率高(分别为 57.5% 和 42.5%),最常见的病理类型为弥漫大 B 细胞淋巴瘤,病变主要累及右侧乳腺。与继发性乳腺恶性血液病相比,原发性乳腺恶性血液病患者具有血小板计数相对更高, $\beta 2$ -MG 水平更低,往往不伴 B 症状,Ann Arbor 分期主要为 I-II 期,骨髓不受累,且生存期显著延长等特点。此外,恶性血液病累及骨髓提示预后不良。

关键词:乳腺血液恶性肿瘤;病理类型;临床特征;生存分析

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Hematologic Malignancies of the Breast: A Investigating Pathological Subtypes, Clinical Characteristics and Prognosis*

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ABSTRACT Objectives: To investigate pathological subtypes, clinical characteristics and prognosis of patients with breast hematological malignancies. **Methods:** We conducted a retrospective review of Xijing Hospital of Air Force Medical University for hematological malignancies diagnosed in breast tissue from Jan.2014 to Jan.2019). Pathological subtypes, clinical characteristics, and patient outcomes were analyzed. **Results:** We identified 33 cases, 32 of them were female, with a mean age of 45.5 years (12-78years). By pathological diagnosis of 30 cases were lymphomas which included 29 (29/33, 87.9%) Non-Hodgkin lymphoma (NHL) and 1(1/33, 3.0%) Hodgkin lymphoma and 3 (3/33, 9.1%) were recurrence of acute leukemias. The 29 NHL cases included 18 (18/29, 62.1%) diffuse large B-cell lymphomas (DLBCLs), 3 (3/29, 10.3%) NK/T cell lymphomas, 2 (2/29, 6.8%) B lymphoblastic leukemia/ lymphomas (B-ALL/LBLs), 1 (1/29, 3.4%) each of follicular lymphoma (FL), Burkitt lymphoma, primary cutaneous anaplastic large cell lymphoma (C-ALCL) and 3 (3/29, 10.3%) lymphomas-not otherwise specified. In total, 9 (57.6%) cases were primary, which were all lymphomas, and 14 (42.4%) cases were secondary to the breast. Our study showed the lesions were mainly involved in the right breast (18/33, 54.5%), followed by the left breast (10/33, 30.3%), and were rarely involved in both sides(5/33, 15.2%). 19 primary cases had higher platelet count ($P=0.004$), significantly lower $\beta 2$ -MG ($P=0.049$), less B symptoms($P=0.017$)and bone marrow involvement($P<0.01$), more were Ann Arbor stage I-II ($P<0.01$) than secondary ones. Significant statistical difference in OS is shown between primary cases and secondary ones ($HR=9.846, P=0.002$). Patients with marrow involvement had worse overall survival (OS) than those without marrow involvement ($HR=6.434, P<$

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0.01)。 **Conclusions:** The majority of breast hematological malignancies patients are middle-aged females. Primary hematological malignancies of the breast are more common than secondary ones: 57.5 % versus 42.5%. Our study showed that the most common hematological malignancy was DLBCL, with the right breast mass as the main clinical manifestation. Primary cases had significant higher platelet count, lower β 2-MG, less B symptoms and bone marrow involvement, more were Ann Arbor stage I-II than secondary ones. Moreover, primary cases had better OS than secondary ones. Patients with marrow involvement was associated with an inferior outcome.

Key words: Breast of hematologic malignancies; Pathological subtypes; Clinical characteristics; Survival analysis

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前言

乳腺恶性血液病非常罕见的,在乳腺肿瘤中占比不到1%^[1,2],多见于55至60岁的女性,偶有男性的个案报道^[3-5]。大多数情况下,乳腺恶性血液病的临床表现没有特异性,以单侧乳腺无痛性肿块为主要症状,很难与早期乳腺癌相鉴别,但一般不会出现乳头溢液、“橘皮样改变”等晚期乳腺的特征性变化,却会因恶性血液病进展表现为发热、贫血、出血、淋巴结肿大等^[6]。影像学不能提供可用于鉴别乳腺癌和乳腺血液肿瘤的具体特征^[7,8],疾病性质的确定仍依赖于组织病理和免疫组化。

乳腺恶性血液病包括白血病及髓系肉瘤、淋巴瘤、浆细胞瘤等,其中最常见的病理类型是淋巴瘤和白血病^[9-11]。乳腺淋巴瘤占乳腺恶性肿瘤的0.04%-0.5%,非霍奇金淋巴瘤(Non-Hodgkin lymphomas, NHL)的1%,结外淋巴瘤的1%-2%^[12,13]。髓样肉瘤^[11,14]、浆细胞瘤^[15,16]等乳腺恶性血液病非常罕见。乳房植入相关间变性大细胞淋巴瘤(Breast Implant Associated Anaplastic Large Cell Lymphoma, BIA-ALCL)是一种罕见的并发症,主要与乳腺植入物有关^[17-19]。

乳腺恶性血液病患者的预后取决于疾病性质、临床分期等。与乳腺癌不同,大多数乳腺恶性血液病患者并不需要手术治疗,被误诊为乳腺癌的血液病患者可能会接受乳腺以及淋巴结切除手术和“不恰当”的化疗,从而导致患者存活率更低^[20]。目前,乳腺恶性血液病的主要治疗手段是根据血液病性质行化疗、放疗、造血干细胞移植等,与乳腺癌存在显著差异。因此,本研究主要分析了乳腺恶性血液病患者的临床特征、实验室特点以及生存状况,结果报道如下。

1 资料与方法

1.1 研究对象

收集自2014年1月至2019年1月空军军医大学西京医院收治的33例乳腺恶性血液病患者的资料,回顾性分析其临床特征、实验室数据和生存状况,并根据2001至2016版WHO诊断标准,白血病经骨髓MICM(细胞学、流式免疫分型、细胞遗传学、分子生物学)确诊,淋巴瘤经组织病理与免疫组化确诊。

1.2 观察指标

分析病史资料、临床信息、病理亚型以及生存状况。其中,白血病患者需完善外周血涂片、骨髓MICM;淋巴瘤患者按照Wiseman标准^[21]进行原发性或继发性分类,监测B症状、乳酸脱氢酶(LDH)、铁蛋白、 β 2-微球蛋白(β 2-MG)、Ann Arbor分期、ECOG评分、IPI评分等指标。

1.3 治疗及疗效评价

在33例患者中,4例行乳房根治术,29例行乳房肿块穿刺活检术,均经组织病理及免疫组化确诊。急性髓系白血病(Acute myeloid leukemia, AML)、B细胞急性淋巴细胞白血病(B cell acute lymphocytic leukemia, B-ALL)、霍奇金淋巴瘤(Hodgkin's lymphoma, HL)、NHL等均按照指南治疗。

1.4 随访及统计学处理

采用邮件、电话、微信等方式进行随访,随访时间截至2019年6月30日。采用SPSS19.0统计软件进行分析,计量资料采用独立样本t检验,计数资料采用 χ^2 检验进行差异性检验,以Kaplan Meier法,Log-rank检验进行生存分析, $P < 0.05$ 表示差异有统计学意义。

2 结果

2.1 病理分类

经病理确诊的乳腺恶性血液病中,29例(29/33, 87.9%)为NHL,其中最常见的是弥漫大B细胞淋巴瘤(Diffuse large B-cell lymphoma, DLBCL)18例(62.1%);NK/T细胞淋巴瘤(NK/T cell lymphoma)3例(10.3%);伯基特淋巴瘤(Burkitt lymphoma, BL)、滤泡(Follicular lymphoma, FL)、原发皮肤间变大细胞淋巴瘤(Primary cutaneous anaplastic large cell lymphoma, C-ALCL)、HL结节硬化型各1例(3.4%),B淋巴瘤母细胞白血病/淋巴瘤(B lymphoblastic leukemia/lymphoma, B-ALL/LBL)2例(6.8%),2例B-NHL(6.8%),1例T-NHL(3.4%)均未进一步分型。ALL复发累及乳腺1例(3.0%),AML复发累及乳腺2例(6.1%)(见表1)。

2.2 原发性和继发性乳腺恶性血液肿瘤

经Wiseman和Liao提出,Hugh等人修改,原发性乳腺淋巴瘤(Primary breast lymphoma, PBL)定义为乳腺组织病理为淋巴瘤,而无淋巴瘤前驱病史,除同侧腋窝淋巴结外无其它部位累及^[21,22],而相对宽泛的定义包括淋巴瘤累及锁骨上和乳腺内部淋巴结,双侧乳腺受累而无区域淋巴结以外远端区域受累的证据^[12]。继发性乳腺淋巴瘤(Secundary breast lymphoma, SBL)定义为同时或随后累及乳腺的全身性淋巴瘤。结合上述定义,本研究中19例原发性恶性血液病患者均为PBL,病变主要累及右侧乳腺(12例,63.2%),左侧相对较少(6例,31.6%),仅有1例(5.2%)是双侧乳腺受累。14例继发性患者,7例为DLBCL,3例AL复发,2例B-ALL/LBL, NK/T、非分类B各1例,主要累及右侧乳腺(6例,42.8%),左侧和双侧乳腺均为4例(28.6%)(表1)。

2.3 临床特点及实验室特征

33例患者中,女性32例(97.0%),男性1例(3.0%),平均年龄为45.5岁(12-78岁)。与14例继发性乳腺恶性血液病患者相

比,19例PBL患者血红蛋白略高,但是无统计学差异($P=0.08$);血小板计数显著升高($P=0.004$), $\beta 2$ -MG显著降低($P=0.049$),而白细胞计数、乳酸脱氢酶、铁蛋白等无明显差异。在19例PLB患者中,5例有B症状,Ann Arbor分期主要为I-II期;而在14例继发性患者中,10例原发病累及骨髓,其中9例淋巴瘤,7例

有B症状,Ann Arbor分期主要为III-IV期。原发性与继发性乳腺恶性血液病在B症状($\chi^2=6.604, P=0.017$)、Ann Arbor分期($\chi^2=25.909, P<0.01$)、骨髓累及($\chi^2=19.472, P<0.01$),其均存在显著统计学差异(表2)。

表1 乳腺恶性血液病患者的病理类型及临床资料

Table 1 Pathological subtypes and clinical characteristics of patients with breast hematological malignancies

Diagnosis	NO.	Sex (F/M)	Age Median (Rang)	Position	Size (cm)	Primary/ Secondary	Treatment
NHL							
DLBCL	18	17/1	59 (20-78)	11 right 7 left	1.5× 1.0-10.0× 8.5	11/ 7	Surgery, Radiotherapy, Chemotherapy
BL	1	1/0	56	left	1.0× 1.0	1/0	Surgery, Chemotherapy
FL	1	1/0	48	right	5.0× 3.5	1/0	Surgery, Chemotherapy
NK/T	3	3/0	46 (12-64)	2 right 1 left	2.0× 2.0-7.0× 5.0	2/1	Chemotherapy
C-ALCL	1	1/0	50	right	3.4× 1.5	1/0	Chemotherapy
T-NHL	1	1/0	55	right	3.6× 1.7	1/0	Surgery and Supportive Therapy
B-NHL	2	2/0	39.5	1 right 1 left	3.0× 2.0-8.5× 6.0	1/1	Surgery, Chemotherapy
HL	1	1/0	32	bilateral	3.0× 2.0	1/0	Chemotherapy
B-ALL/LBL	2	2/0	30	1 right 1 left	3.0× 2.5	0/2	Surgery, Chemotherapy
ALL	1	1/0	46	bilateral	3.5× 4.0	0/1	Chemotherapy
AML	2	2/0	32.5	1 bilateral 1 left	5.0× 4.5-10.0× 6.5	0/2	Chemotherapy

Note: NHL, non-Hodgkin lymphoma; B-NHL, B cell NHL; T-NHL, T cell NHL; DLBCL, diffuse large B-cell lymphoma; BL, Burkitt lymphoma; FL, follicular lymphoma; NK/T, NK/T cell lymphoma; C-ALCL, primary cutaneous anaplastic large cell lymphoma; HL, Hodgkin lymphoma; B-ALL/LBL, B lymphoblastic leukemia/ lymphoma; ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia.

表2 乳腺恶性血液病患者的实验室数据

Table 2 Laboratory data of patients with breast hematological malignancies

Diagnosis	Primary Hematologic Malignancies	Secondary Hematologic Malignancies	<i>P</i>
	n=19	n=14	
	(Median, Rang)	(Median, Rang)	
	B-NHL (n=14), T-NHL (n=4), HL(n=1)	B-NHL(n=8), T-NHL (n=1), AL(n=3), B-ALL/LBL(n=2)	
WBC($10^9/L$)	6.0(3.06-14.57)	4.9(1.5-30.63)	0.536
HB(g/L)	127.5(78.0-141.0)	118(60.0-145.0)	0.08
PLT($10^9/L$)	228(47.0-627.0)	136(6.0-238.0)	0.004
LDH(U/L)	187(101-1705)	284(143.0-907.0)	0.473
$\beta 2$ -MG(mg/L)	1.72(1.14-5.17)	3.07(2.28-8.53)	0.049
Ferritin($\mu g/L$)	107.0(39.3-947.0)	106.0(38.7-185.0)	0.220
B symptom	5/19	7/9	0.017
Ann Arbor	I - II : 19 III-IV : 0	I - II : 1 III-IV : 8	<0.01
Bone marrow involvement	0/19	10/14	<0.01

Note: B-NHL, B cell NHL; T-NHL, T cell NHL; HL, Hodgkin lymphoma; B-ALL/LBL, B lymphoblastic leukemia/ lymphoma; AL, acute leukemia. WBC, white blood cell count; HB, hemoglobin; PLT, platelet count, LDH, lactate dehydrogenase.

2.4 生存分析

本研究的 33 例患者,4 例经乳腺根治术后确诊,术后 2 例仅接受对症支持治疗,2 例行化疗;29 例患者经乳房肿块穿刺确诊,23 例仅行化疗,3 例联合放疗,3 例联合造血干细胞移植治疗。19 例 PBL 患者平均随访时间 36 个月(6-60 个月),18 人存活,1 例眼部复发,2 例中枢神经系统复发,其中 1 人死亡。在

14 例继发患者中,平均随访时间 14.4 个月(2-60 个月),6 人存活,8 人死亡。原发性乳腺恶性血液病患者与继发患者相比,其生存期显著延长,具有统计学差异 ($HR=9.846, P=0.002$, 图 1A)。恶性血液病累及骨髓与未累及骨髓的患者相比,生存期显著缩短($HR=6.434, P<0.01$, 图 1B)。

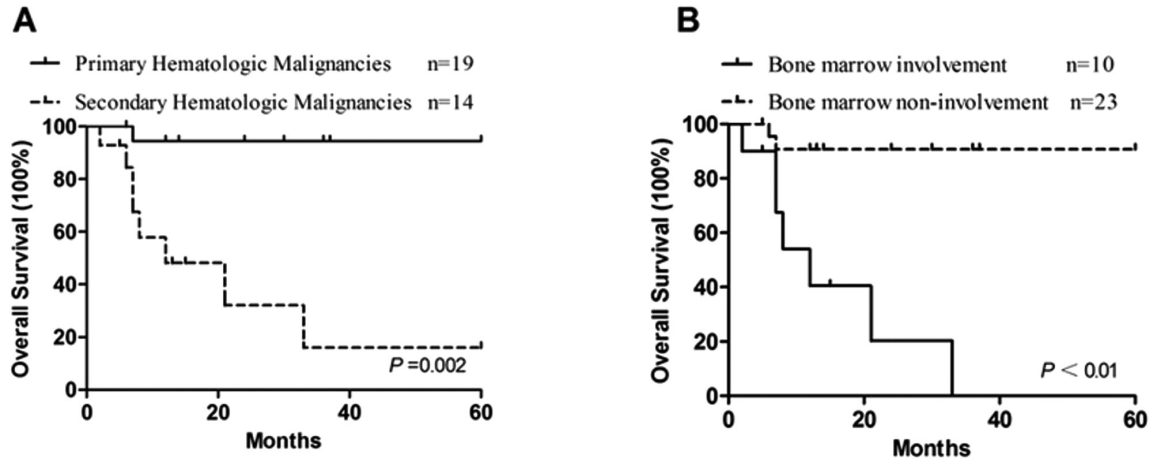


图 1 乳腺恶性血液病患者的生存分析

Fig.1 Kaplan-Meier survival analysis of patients with breast hematological malignancies

3 讨论

本研究中绝大多数乳腺恶性血液病患者为女性,只有 1 名男性被诊断为 DLBCL, 与之前研究报道的原发乳腺血液病发生在男性是轶事,且病理类型多为 DLBCL 一致^[6]。此外,还有 FL、MZL 等少数病例报道^[3,23]。乳腺恶性血液病可分为原发性和继发性,本研究中原发性乳腺血液肿瘤比继发性发生率更高(分别为 57.5%和 42.4%),这与之前的研究结果一致^[11,20,24]。原发性乳腺恶性血液病多表现为乳腺肿块形成,继发性乳腺恶性血液病除乳腺肿块外,还有发热、盗汗、淋巴结肿大、贫血等全身症状^[25]。实际上,往往很难区分原发性乳腺恶性血液病伴继发转移,还是继发性乳腺受累,或者血液病合并乳腺疾病,且由于症状的非特异性,继发性乳腺血液病的诊断存在挑战。

在本研究中,无论是原发性还是继发性乳腺血液病,病变主要累及右侧乳腺。这与许多研究报道的“无法解释的右乳优势”相同^[11,26],但也有研究并不支持这一发现^[27]。病理分型中,NHL 最常见,而 DLBCL 显著高于其它亚型,这与之前研究一致^[2,13,26,28]。本研究结果显示与继发性患者相比,原发性乳腺恶性血液病患者血小板计数显著增高和 $\beta 2$ -MG 水平显著降低,而白细胞计数、血红蛋白、乳酸脱氢酶、铁蛋白等无明显差异。B 症状、Ann Arbor 分期、骨髓累及的显著统计学差异提示继发性乳腺恶性血液病风险更大。

大多数研究表明手术切除不能使乳腺恶性血液病患者获益。随着穿刺活检技术推广,手术切除并不是必须的,目前仅进行最低限度的手术以便确定组织学诊断^[29],主要治疗手段包括化疗、放疗以及造血干细胞移植治疗等^[30]。在本研究中,因仅行手术治疗患者例数少,无法评估手术切除的价值。与原发性乳腺恶性血液病患者相比,继发性患者具有疾病分期多为晚期(淋巴瘤 III-IV)、常伴有全身症状、血液病多累及骨髓、相关并发

症多等临床特点,因此继发患者生存期显著缩短是十分容易理解的。恶性血液病累及骨髓可影响骨髓正常造血,可出现感染、贫血、出血等症状,不仅导致患者治疗耐受性差,还极大影响化疗方案和药物剂量,综合多方面因素导致此类患者预后不良。

综上所述,乳腺恶性血液病患者以中年女性为主,原发性乳腺恶性血液病比继发性发病率高,最常见的病理类型为 DLBCL,病变主要累及右侧乳腺。与继发性乳腺恶性血液病患者相比,原发性乳腺恶性血液病患者的血小板计数相对更高, $\beta 2$ -MG 水平更低,往往不伴 B 症状,Ann Arbor 分期早,骨髓不受累,且生存期显著延长。此外,恶性血液病累及骨髓提示不良预后。

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