

## 白塞病合并8号染色体三体22例分析及文献复习

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**【摘要】** 目的 探讨分析8号染色体三体异常白塞病(Behcet's disease, BD)患者的临床特点。方法 分析2012年10月至2020年7月复旦大学附属华东医院收治的22例8号染色体三体BD的住院患者,并检索中英文文献库中BD合并8号染色体三体的患者共46例,对临床特点进行比较分析。结果 22例8号染色体三体的BD患者中,男5例、女17例;平均发病年龄( $45.6 \pm 11.4$ )岁。临床特点包括复发性口腔溃疡(100%),外周血细胞减少(100%),外阴溃疡(86.4%),皮肤损害(63.6%),针刺反应阳性(46.4%)和关节炎(27.3%)。所有患者均出现骨髓细胞形态学的异常,5例表现符合骨髓增生异常综合征(myelodysplastic syndromes, MDS)(22.7%),15例合并肠道溃疡(68.2%),1例(4.5%)头颅MRI发现左侧小脑半球异常信号灶(约20 mm×15 mm)、灶周水肿,可能为低级别胶质瘤所有患者均无眼睛、心脏和血管受累。与文献检索的46例患者比较,我院收治的22例患者仅合并MDS的比例不同( $P < 0.001$ ),其余表现均相符。5例患者表现符合MDS(22.7%),其余17例患者表现出不同程度的骨髓细胞形态异常,合并MDS与不合并MDS患者临床指标进行比较,血红蛋白有显著差异( $P < 0.05$ ),发病年龄、性别、肠溃疡、白细胞、血小板、ESR、CRP等均无明显差异。与不合并8号染色体三体BD的患者比较,合并8号染色体三体的患者女性占多数( $P = 0.040$ ),眼睛损害少见( $P = 0.033$ ),肠溃疡多发( $P < 0.001$ )以及更易合并MDS( $P < 0.001$ ),两组患者的口腔溃疡、外阴溃疡、关节炎、皮肤损害、神经系统病变、血管病变以及心脏病变均无显著差异。结论 8号染色体三体的BD患者常见外周血细胞减少症和肠溃疡,在诊断、治疗及预后均有别于典型的BD或MDS。

**【关键词】** 白塞病(BD); 8号染色体三体; 骨髓增生异常综合征(MDS); 肠溃疡

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## Analysis of 22 cases of Behcet's disease associated with trisomy 8 and literature review

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**【Abstract】** **Objective** To investigate the clinical characteristics of trisomy 8 in the pathogenesis of Behcet's disease (BD). **Methods** We analyzed 22 BD with trisomy 8 patients admitted to Huadong Hospital, Fudan University from Oct 2012 to Jul 2020, and retrieved 46 cases of BD combined with trisomy 8 from Chinese and English literature database, the clinical characteristics were compared and analyzed. **Results** Among 22 BD patients with trisomy 8, there were 5 males and 17 females, and the mean age of onset was ( $45.6 \pm 11.4$ ) years. The clinical features included recurrent oral ulcers (100%), peripheral blood loss (100%), vulvar ulcers (86.4%), skin lesions (63.6%), positive acupuncture reaction (46.4%) and arthritis (27.3%). Myelodysplastic syndromes (MDS) were found in 5 patients (22.7%), intestinal ulcers in 15 patients (68.2%), and MRI of one patient (4.5%) showed abnormal signal foci in the left cerebellum

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(20 mm×15 mm), with slight edema around the foci, and possibly gliomas. No ocular, cardiac or vascular involvement was found in all patients. Compared with 46 patients from literature search, the rate of MDS was different ( $P<0.001$ ), the other manifestations were consistent. Five patients showed MDS (22.7%), and the other 17 patients showed abnormal bone marrow cells in different degrees. Between MDS and no MDS patients, there was significant difference in hemoglobin ( $P<0.05$ ), but no significant differences in age, sex, intestinal ulcer, white blood cell, platelet, ESR and CRP. Compared with BD without trisomy 8, women were more common in group of BD with trisomy 8 ( $P=0.040$ ), less eye damage ( $P=0.033$ ), more intestinal ulcers ( $P<0.001$ ) and were more likely to complicated with MDS ( $P<0.001$ ) in group of BD with trisomy 8. There were no significant differences in oral ulcers, vulvar ulcers, arthritis, skin lesions, nervous system lesions, vascular lesions and heart disease between patients with and without trisomy 8.

**Conclusion** BD with trisomy 8 patients are more likely to suffer from peripheral blood cytopenia and intestinal ulcers. The pathogenesis of BD with trisomy 8 is unknown, which is different from typical BD and MDS in diagnosis, treatment and prognosis.

**【Key words】** Behcet's disease (BD); trisomy 8; myelodysplastic syndromes (MDS); intestinal ulcers

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白塞病(Behcet's disease, BD)是一种以复发性口腔溃疡为首发、逐渐伴发外阴溃疡、结节性红斑等皮肤黏膜病变为基本临床特征,可能选择性发生眼炎、肠溃疡、主动脉瓣反流、静脉血栓、动脉狭窄、动脉瘤、关节炎或血细胞减少症等1~2个寡器官损害的变异性血管炎。在“丝绸之路”沿线国家的发病率较高,其中东亚的发病率为(13.5~20)/100 000<sup>[1]</sup>。骨髓增生异常综合征(myelodysplastic syndromes, MDS)是一种以骨髓造血细胞异常导致外周血细胞减少的血液系统疾病<sup>[2]</sup>, 8号染色体三体是MDS中最常见的一种染色体数目异常。目前国内关于BD合并8号染色体三体的报道尚不多见,其发病机制及临床特点亦不明确。本文总结复旦大学附属华东医院风湿科收治的22例BD合并8号染色体三体患者,与1 236例不合并8号染色体三体的BD患者进行比较,并检索中英文文献库,筛选8号染色体三体BD患者46例,对比分析其临床特点,探讨8号染色体三体异常与BD临床特点的相关性,提高临床医师对该类疾病的关注。

## 资 料 和 方 法

**研究对象** 收集2012年10月至2020年7月在复旦大学附属华东医院风湿免疫科住院的BD患者

1 258例,对存在一系或多系血细胞异常的患者进行骨髓穿刺,筛选出8号染色体三体的病例,共计22例,分析其临床特点并随访。并通过文献库检索,总结8号染色体三体的BD患者46例。所有病例均符合2013年BD国际诊断标准(international criteria for Behcet's disease, ICB<sub>D</sub>),根据患者的症状和体征进行评分,所有患者得分均 $\geq 4$ 分<sup>[3]</sup>。通过骨髓染色体及FISH检查明确8号染色体三体。本研究得到复旦大学附属华东医院伦理委员会批准(批准号:2018K003),入选者均签署知情同意书。

**研究方法** 以“白塞病”与“8号染色体三体”为检索词,检索万方、维普、中国知网数据库,以“Behcet's disease”与“trisomy 8”为检索词在PubMed中进行检索,筛选出8号染色体三体的病例。与本研究22例8号染色体三体的病例汇总,记录每一病例的性别、年龄、发病年龄、病程、包括并发症在内的所有临床表现,并进行对比分析。

**统计学处理** 采用SPSS 19.0软件进行统计学分析。计量资料以 $\bar{x}\pm s$ 表示,采用 $t$ 检验;计数资料采用 $\chi^2$ 检验。 $P<0.05$ 为差异有统计学意义。

## 结 果

**一般资料** 22例BD合并8号染色体三体的患

者中,男性5例,女性17例;平均发病年龄( $45.6 \pm 11.4$ )岁;文献库检索到的46例患者中,男性22例,女性24例,平均发病年龄为( $49.6 \pm 18.3$ )岁。

**临床表现** 22例患者均存在口腔溃疡;19例患者有外阴溃疡(86.4%);14例患者有皮疹(63.6%),主要以结节性红斑、毛囊炎及脓疱疹为主;8例患者针刺反应阳性(46.4%);6例患者存在关节肿痛,并经关节超声检查证实有关节炎(27.3%),以单侧膝关节、肘关节为主;22例患者均出现骨髓细胞形态学的异常,5例表现符合MDS(22.7%);15例患者存在肠溃疡(68.2%),其中1例患者因腹痛就诊发现溃疡穿孔行手术治疗,术后出现肠梗阻行二次手术,其余患者均无明显腹痛、腹泻、便血等症状;1例

患者头颅MRI发现左侧小脑半球异常信号灶(约 $20\text{ mm} \times 15\text{ mm}$ ),病灶周围水肿,可能为低级别胶质瘤,无神经系统症状。所有患者外周血管B超、心超均未见异常。我科收住的22例BD合并8号染色体三体的患者与文献库中检索到的46例患者相比较,仅合并MDS的比例不同( $P=0.000$ ),其余表现均相符(表1)。与不合并8号染色体三体的1 236例BD患者比较,合并8号染色体三体的患者女性占多数( $P=0.040$ ),眼睛损害少见( $P=0.033$ ),肠溃疡多发( $P<0.001$ )以及更易合并MDS( $P<0.001$ ),两组患者的口腔溃疡、外阴溃疡、关节炎、皮肤损害、神经系统病变、血管病变以及心脏病变均无显著差异(表2)。

表1 本研究与文献库检索8号染色体三体的BD患者比较

Tab 1 Comparison between the patients of the present study and those from the literature [ $(\bar{x} \pm s)$  or  $n(\%)$ ]

Characteristics	BD with trisomy 8 (our group, $n=22$ )	BD with trisomy 8 (in literature, $n=46$ )	$t$ or $\chi^2$	$P$
Age at BD diagnosis (y)	$45.6 \pm 11.4$	$49.6 \pm 18.3$	-0.621	0.968
Male/Female	5/17	22/24	3.916	0.063
Oral ulcer	22 (100)	46 (100)	-	-
Genital ulcer	19 (86.4)	37 (80.4)	0.360	0.498
Ocular lesion	0 (0)	3 (6.5)	1.501	0.546
Skin lesions	14 (63.6)	27 (58.7)	0.152	0.595
Positive pathergy test	8 (46.4)	22 (47.8)	0.793	0.373
Arthritis	6 (27.3)	10 (21.7)	0.253	0.685
Central nervous system	1 (4.5)	0 (0)	2.122	0.154
Vascular lesions	0 (0)	6 (13)	3.147	0.166
Cardiac involvement	0 (0)	0 (0)	-	-
Intestinal ulcers	15 (68.2)	36 (78.3)	0.806	0.552
Abnormal morphology of bone marrow cells	22 (100)	46 (100)	-	-
MDS	5 (22.7)	44 (100)	35.770	<b>&lt;0.001</b>

表2 BD合并8号染色体三体与不合并8号染色体三体临床表现比较

Tab 2 Clinical characteristics between the patients of BD with trisomy 8 and BD without trisomy 8 [ $n(\%)$ ]

Characteristics	BD with trisomy 8 ( $n=22$ )	BD with trisomy 8 ( $n=1\ 236$ )	$\chi^2$	$P$
Male/Female	5/17	667/569	8.476	<b>0.040</b>
Oral ulcer	22 (100)	1147 (91.0)	1.705	0.192
Genital ulcer	19 (86.4)	850 (67.2)	3.132	0.077
Ocular lesion	0 (0)	179 (14.5)	3.715	<b>0.033</b>
Skin lesions	14 (63.6)	637 (50.4)	1.267	0.260
Arthritis	6 (27.3)	245 (19.3)	0.751	0.386
Central nervous system	1 (4.5)	35 (2.8)	0.228	0.633
Vascular lesions	0 (0)	69 (5.6)	1.299	0.254
Cardiac involvement	0 (0)	41 (3.3)	0.754	0.385
Intestinal ulcers	15 (68.2)	160 (12.9)	55.070	<b>&lt;0.001</b>
MDS	5 (22.7)	15 (1.2)	63.944	<b>&lt;0.001</b>

**实验室指标** 22例患者均出现1系或多系血细胞减少,其中16例外周血白细胞减少,17例外周血血红蛋白减少,14例外周血血小板减少。对22例患者实验室指标进行统计,WBC为 $(3.3 \pm 1.9) \times 10^9/L$ ; Hb为 $(102.5 \pm 16.9) g/L$ ; PLT为 $(121.1 \pm 92.5) \times 10^9/L$ ; 炎症指标明显升高[ESR为 $(45.2 \pm 35.2) mm/h$ , CRP为 $(24.5 \pm 32.6) mg/L$ , SAA为 $(77.2 \pm 87.7) mg/L$ , IL-6为 $(23.5 \pm 49.1) pg/mL$ , 铁蛋白为 $(267.9 \pm 264.3) ng/mL$ ]; 谷丙转氨酶及肌酐均无明显异常[ALT为 $(19.2 \pm 12.1) U/L$ ; Cr为 $(57.6 \pm 16.9) \mu mol/L$ ]; 3例T-SPOT阳性; ANA均为阴

性。22例患者均有染色体异常,1例骨髓染色体检查为49,XX,+7,+8,+15[6]/48,XX,+7,+8[4],1例49,XY,+8,+9,其余20例均为47,XX,+8/47,XY,+8; FISH检查均显示Vysis CEP8阳性(+8)。

22例患者均出现不同程度的骨髓细胞形态学的异常,5例表现符合MDS(22.7%),其余17例多次复查骨穿结果呈现变化,有向MDS进展的趋势。合并或不合并MDS的患者临床指标比较,血红蛋白有显著差异( $P < 0.05$ ),发病年龄、性别、肠溃疡、白细胞、血小板、ESR、CRP等均无明显差异(表3)。

表3 8号染色体三体的BD合并与不合并MDS的比较

Tab 3 Comparison between the patients of BD-trisomy 8 with MDS and BD-trisomy 8 without MDS  $[(\bar{x} \pm s) \text{ or } n(\%)]$

Characteristics	BD-trisomy 8 with MDS ( $n=5$ )	BD-trisomy 8 without MDS ( $n=17$ )	$t$ or $\chi^2$	$P$
Age at BD diagnosis (years)	$51.8 \pm 11.6$	$43.8 \pm 11.1$	-1.413	0.173
Male/Female	1/4	4/13	0.027	0.687
Intestinal ulcers	5 (100)	10 (58.8)	3.020	0.082
WBC ( $10^9/L$ )	$3.9 \pm 2.2$	$3.1 \pm 1.8$	-0.736	0.470
Hemoglobin (g/L)	$87.4 \pm 12.9$	$107.0 \pm 15.4$	2.573	<b>0.018</b>
Platelets ( $10^9/L$ )	$73.4 \pm 44.0$	$44.0 \pm 99.1$	1.336	0.197
ESR (mm/h)	$69.0 \pm 38.2$	$38.2 \pm 30.1$	-1.811	0.085
CRP (mg/L)	$34.4 \pm 46.2$	$21.6 \pm 28.7$	-0.766	0.453

WBC: White blood cell; ESR: Erythrocyte sedimentation; CRP: C-reactive protein.

**治疗及随访** 15例合并肠溃疡的患者予以沙利度胺、环孢素、激素以及英夫利昔单抗治疗,1例患者用药过程中出现严重肺部感染,停用英夫利昔单抗,继续口服药物治疗;1例患者出院后未再就诊;6例患者口服沙利度胺、环孢素及激素治疗。至2020年7月,18例患者病情稳定继续治疗随访中,3例患者因出血或肺部感染死亡,1例患者失访。

## 讨 论

BD是一种可累及全身多个器官的慢性炎症性疾病,1937年土耳其皮肤科医师Behcet's首次报道<sup>[4]</sup>。目前尚无特异性血清指标,主要依据临床症状进行诊断。MDS是一种恶性克隆性疾病,由造血干、祖细胞发育异常所引起,8号染色体三体是MDS中最常见的一种染色体数目异常。研究发现8号三体与骨髓原始细胞危象、嗜酸细胞增多症的发生有着密切联系<sup>[5]</sup>。根据国际预后指数修改版(IPSS-R)标准,8号染色体三体被归为MDS的细胞遗传危险因素<sup>[6]</sup>。有研究<sup>[7]</sup>显示8号染色体三体的形成可能与

NQO1酶缺陷相关。8号染色体三体BD合并MDS的报道多分布于韩国和日本<sup>[8-10]</sup>,国内相关报道相对较少,本文拟阐述BD合并8号染色体三体患者的临床特点,提高临床医师对其认识。

本文22例8号染色体三体BD患者MDS的发生率为22.7%,其余患者目前虽尚不能诊断为MDS,但均出现不同程度的骨髓造血异常,存在发展为MDS的可能,需长期随访。8号染色体三体异常可能是BD患者并发MDS的高危因素。根据已有的22例患者并结合相关文献检索可发现,8号染色体三体的BD患者更易合并MDS,更易累及肠道,而眼睛、心脏、血管、神经系统、关节很少累及<sup>[11-12]</sup>。既往文献表明,BD合并MDS患者肠道损害的发生率(77.3%)明显高于单纯BD患者(15.5%)<sup>[9,13]</sup>。本研究小组曾对2013年10月至2015年10月住院确诊为BD的375例患者进行分析统计,存在消化道损害的患者有44例(11.7%)<sup>[14]</sup>,而本次统计的不合并8号染色体三体的BD患者中,肠溃疡的患者有160例(12.9%),22例8号染色体三体异常的BD患者的消化道损害的发生率明显升高



(68.2%),这一结果也与既往文献报道相符<sup>[15-18]</sup>。

8号染色体三体与BD患者出现肠道累及有一定联系,但其机制尚不清楚。有文献对具有8号染色体三体异常的MDS患者进行研究分析,发现部分细胞因子的表达明显升高,包括转化生长因子- $\beta$ 、干扰素- $\beta$ 2、IL-6和IL-7R等,而这些因子都参与了免疫和炎症活动<sup>[19]</sup>。BD是一种慢性炎症性疾病,存在多种细胞因子的异常,包括IL-1 $\beta$ 、IL-6、IL-8、IL-17和TNF- $\alpha$ 等<sup>[20]</sup>。BD合并8号染色体三体患者的血清中存在特殊的细胞因子,血清中细胞因子G-CSF、IL-6、IL-8、TNF- $\alpha$ 均明显升高<sup>[21]</sup>。8号染色体上存在多种基因,如IL-7、小诱导因子A5(RANTES)、TNF受体超家族等<sup>[22]</sup>,这些基因编码的炎症因子的过度表达可能与BD的发病相关。可以推测BD和8号染色体三体可能起源于同一免疫异常,造成骨髓造血干细胞破坏导致MDS,引起其他组织和器官的损害。

目前对于BD合并8号染色体三体异常患者尚无特效治疗方法,考虑到炎症因子在其中发挥一定作用,通常在常规BD治疗基础上调整剂量或合用生物制剂<sup>[19-20,23-25]</sup>。在BD合并MDS、8号染色体三体异常的患者中,肠道损害是较常见的症状,病情重且治疗困难<sup>[26-27]</sup>。对于出现肠道累及的患者,可在增加常规药物剂量的基础上,延长生物制剂使用时间,预后方面个体差异性大。

综上所述,8号染色体三体的BD合并肠溃疡可能是一种新的综合征,目前致病机制不明,可能是后天基因突变引起的自身炎症性疾病,其诊断、治疗及预后均有别于典型的BD或MDS。BD患者出现一系或多系血细胞异常时,及时进行骨髓细胞形态学、染色体以及FISH检查,有助于早期诊断MDS。对于8号染色体三体异常的BD患者,即使没有消化道症状,也应及早进行肠镜检查以明确消化道病变,对减少消化道溃疡出血、穿孔等并发症的发生有重要意义。

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