

二甲双胍致药物性肝损伤罕见一例并文献复习

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摘要

二甲双胍是治疗2型糖尿病的一线口服药物, 其临床安全性和耐受性普遍良好, 但诱发严重肝毒性的情况极为罕见。本文报道1例62岁女性患者, 因“间断右上腹疼痛伴皮肤及巩膜黄染2月”入院。患者有半年2型糖尿病病史, 长期规律服用二甲双胍治疗(具体剂量不详), 血糖控制尚可。入院检查显示肝功能显著异常: ALT 1223U/L、AST 666U/L、总胆红素99.4 $\mu\text{mol/L}$ 、直接胆红素60 $\mu\text{mol/L}$ 。影像学检查排除胆道梗阻及占位性病变, 肝穿刺活检提示肝细胞弥漫性水肿、坏死及炎症细胞浸润, 符合药物性肝损伤(DILI)特征。根据ALT/ALP (R值 = 3.91), 本例属于混合型偏肝细胞型DILI。结合RUCAM评分10分(极可能), 排除病毒性、自身免疫性肝病等其他病因后, 确诊为二甲双胍所致DILI。停用二甲双胍并给予保肝治疗2周后, 患者症状缓解, 肝功能逐步改善。值得注意的是, 随访期间患者因糖尿病再次使用口服降糖药时, 肝功能短期内再次异常, 提示肝脏对药物存在高度敏感性。本病例提示, 临床使用二甲双胍时需密切监测肝功能, 一旦出现肝损伤相关症状应及时停药并明确病因, 早期识别和干预对改善预后至关重要。

关键词

二甲双胍, 药物性肝损伤, 2型糖尿病, 诊断, 治疗

A Rare Case of Drug-Induced Liver Injury Due to Metformin and Literature Review

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Abstract

Metformin is the first-line oral drug for the treatment of type 2 diabetes mellitus, and its clinical

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safety and tolerability are generally good, but the incidence of severe hepatotoxicity is extremely rare. In this article, we report a case of a 62-year-old female patient who was admitted to the hospital with “intermittent right upper abdominal pain with yellowing of the skin and sclera for 2 months”. The patient had a six-month history of type 2 diabetes mellitus and had been taking metformin regularly for a long period of time (the exact dosage was not known), and her glycemic control was fair. Admission tests showed significant abnormalities in liver function: ALT 1223 U/L, AST 666 U/L, total bilirubin 99.4 $\mu\text{mol/L}$, direct bilirubin 60 $\mu\text{mol/L}$. Imaging studies excluded biliary obstruction and space-occupying lesions, and a liver puncture biopsy showed diffuse edema, necrosis, and inflammatory cell infiltration in hepatocytes, which was consistent with the features of drug-induced liver injury (DILI). According to ALT/ALP (R value = 3.91), this case belonged to mixed partial hepatocellular DILI. Combined with the RUCAM score of 10 (highly probable), the diagnosis of metformin-induced DILI was confirmed after ruling out other etiologies, such as viral and autoimmune liver diseases. After discontinuing metformin and giving hepatoprotective therapy for 2 weeks, the patient’s symptoms were relieved, and her liver function gradually improved. Notably, when the patient was reintroduced to oral hypoglycemic agents for diabetes mellitus during the follow-up period, the liver function became abnormal again in a short period of time, suggesting that there is a high degree of sensitivity of the liver to the drug. This case suggests that liver function should be closely monitored when metformin is used in clinical practice, and once symptoms related to liver injury appear, the drug should be stopped and the etiology of the disease should be clarified, and early identification and intervention are crucial for improving the prognosis.

Keywords

Metformin, Drug-Induced Liver Injury, Type 2 Diabetes Mellitus, Diagnosis, Treatment

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1. 引言

二甲双胍作为双胍类降糖药,已在临床应用超过 60 年。其通过抑制肝糖输出、增强外周组织对葡萄糖的摄取而有效控制血糖[1],在大多数患者中安全性和耐受性良好[2]。然而,近年来少数病例报告指出,二甲双胍其可能引发严重不良反应[3],包括肝脏损伤[4]。药物性肝损伤(DILI)是指由药物或其代谢产物引起的肝脏损伤,其临床表现可从轻度转氨酶升高至急性肝衰竭不等,约占临床肝损伤病因的 10%~15% [5] [6]。根据 ALT 与 ALP 比值(R 值),DILI 可分为肝细胞型($R \geq 5$)、胆汁淤积型($R \leq 2$)及混合型($2 < R < 5$),该分型对判断损伤机制及预后具有重要意义[7]。

尽管二甲双胍的肝毒性在临床中极为罕见,但一旦发生可能导致严重后果[8] [9],需引起临床医师的高度重视。本文通过分析 1 例二甲双胍致严重肝损伤的病例,结合文献复习,详细探讨其临床特征、诊断思路及治疗策略,旨在提高医务人员对该类罕见不良反应的警惕性,促进早期识别和干预,为临床实践提供有价值的参考,并进一步探讨二甲双胍相关肝损伤的机制及防治策略。

2. 病例报告

患者女性,62 岁,因“小便颜色加深、皮肤黄染 2 月”入院。既往 2 型糖尿病病史半年,空腹血糖最高达 17 mmol/l,长期规律服用二甲双胍(具体剂量不详),血糖控制稳定,否认长期饮酒史、基础肝病史及其他慢性病长期用药史。

2月前无明显诱因出现间断右上腹隐痛,呈阵发性,程度可耐受,无放射痛,伴全身皮肤黏膜及巩膜黄染、尿色加深,但无瘙痒、发热或恶心呕吐。外院检查提示肝功能显著异常(AST: 666 U/L; ALT: 1223 U/L, 总胆红素: 99.4 $\mu\text{mol/L}$, 直接胆红素: 60 $\mu\text{mol/L}$),予保肝等对症治疗症状及指标略有改善。半月前复查显示肝功能持续恶化(AST: 392 U/L; ALT: 668 U/L; 直接胆红: 197 $\mu\text{mol/L}$),为行进一步诊治遂转入我院。

患者入院时查体: 体温 36.7℃, 脉搏 78 次/分, 呼吸 18 次/分, 血压 136/82 mmHg; 全身皮肤黏膜及巩膜中度黄染, 右上腹轻度压痛, 无反跳痛, 肝区叩痛(+), 移动性浊音(-)。肝功能检查示: AST: 129 U/L; ALT: 195 U/L; 总胆红素: 311.84 $\mu\text{mol/L}$; 直接胆红素: 216.15 $\mu\text{mol/L}$; ALP 156 U/L; CA19-9: 621 U/mL(见表 1)。血常规、肾功能及电解质基本正常。肝炎病毒标志物、自身免疫性肝病抗体全套均阴性, 排除病毒性及自身免疫性肝病。根据 DILI 分型标准计算 R 值: $(\text{ALT 实测值}/\text{ALT 参考上限}) \div (\text{ALP 实测值}/\text{ALP 参考上限}) = (195/40) \div (156/125) \approx 4.875 \div 1.248 \approx 3.91$, 符合混合型偏肝细胞型 DILI ($2 < R < 5$) [7]。

Table 1. Laboratory test data during the course of treatment
表 1. 治疗过程中实验室检验数据

项目	D1	D5	D11	D16	D19	D22	D27
谷丙转氨酶(U/L)	195.00	181.00	118.00	91.00	66.00	40.00	32.00
谷草转氨酶(U/L)	129.00	193.00	126.00	94.00	70.00	56.00	40.00
直接胆红素($\mu\text{mol/L}$)	216.15	262.50	207.95	141.66	102.19	65.31	49.44
总胆红素($\mu\text{mol/L}$)	311.84	395.65	298.34	194.00	144.97	91.52	68.39
CA19-9 (U/mL)	523.80	621.00	-	324.20	235.80	-	110.00

追问病史, 患者服用二甲双胍半月后出现肝功异常, 且未服用任何其他肝毒性药物, 初步考虑服用二甲双胍所致药物性肝损伤可能, 但因患者已停用 2 月, 肝功仍呈进行性加重且 CA19-9 持续升高, 不排除合并其他原因, 遂计划行 MRCP、增强 CT 及肝穿刺活检进一步明确诊断, 同时给予天晴甘美、还原型谷胱甘肽、思美泰等保肝及对症支持治疗。

入院后考虑不排除肝外胆道梗阻及肿瘤的可能, 故完善上腹部增强 CT 及 MRCP 示未见明显占位性病变, 肝内外胆管无扩张及异常信号影; 肝脏超声示“肝脏回声略粗糙, 考虑肝脏弥漫性病变”(见图 1); 超声胃镜示: 胰腺形态规整, 内部回声均匀, 胰管及胆总管无扩张(见图 2)。为明确诊断, 与患者沟通后行肝脏穿刺活检检查, 结果示: 肝小叶结构欠清晰, 肝细胞排列紊乱, 弥漫性水肿, 轻度淤胆, 可见点状坏死, 汇管区纤维增生及慢性炎细胞浸润, 符合药物性肝损伤的特征。

根据 RUCAM (Roussel Uclaf Causality Assessment Method)评分系统评估: 患者用药后半月出现肝损伤(+2 分), 停药后肝功能显著改善(+3 分), 再次暴露药物后肝功能异常复发(+2 分), 排除其他肝损伤病因(+2 分), 结合二甲双胍致肝损伤的罕见报道(+1 分), 总分为 10 分, 符合“极可能”二甲双胍所致药物性肝损伤的诊断标准[10]。综合上述检查, 排除梗阻性黄疸, 病毒性肝病及自身免疫性肝病, 确诊为二甲双胍致药物性肝损伤。治疗上继续给予上述保肝药物, 加用前列地尔稳定肝细胞、改善肝脏微循环, 促肝细胞生长素注射液促进肝细胞的修复, 严密监测肝功能变化。治疗半月后, 患者症状减轻, 全身皮肤黏膜及巩膜黄染较前好转, 复查肝功能示 ALT: 91.00 U/L, AST: 94.00 U/L, 总胆红素: 94.00 $\mu\text{mol/L}$, 直接胆红素: 141.66 $\mu\text{mol/L}$ 。治疗 1 月后, 肝脏功能基本恢复正常, 无明显不适。

后续患者因糖尿病再次入院时查肝功能正常, 予西格列他钠片、阿卡波糖、达格列净联合胰岛素治疗 1 周后, 肝功能再次异常(ALT: 76 U/L, AST: 63 U/L), 考虑可能是肝脏对药物高度敏感, 遂停用口服

降糖药, 仅予胰岛素控制血糖, 1 周后肝功能恢复正常。3 个月随访期间, 胰岛素控制血糖良好, 肝功能持续正常。

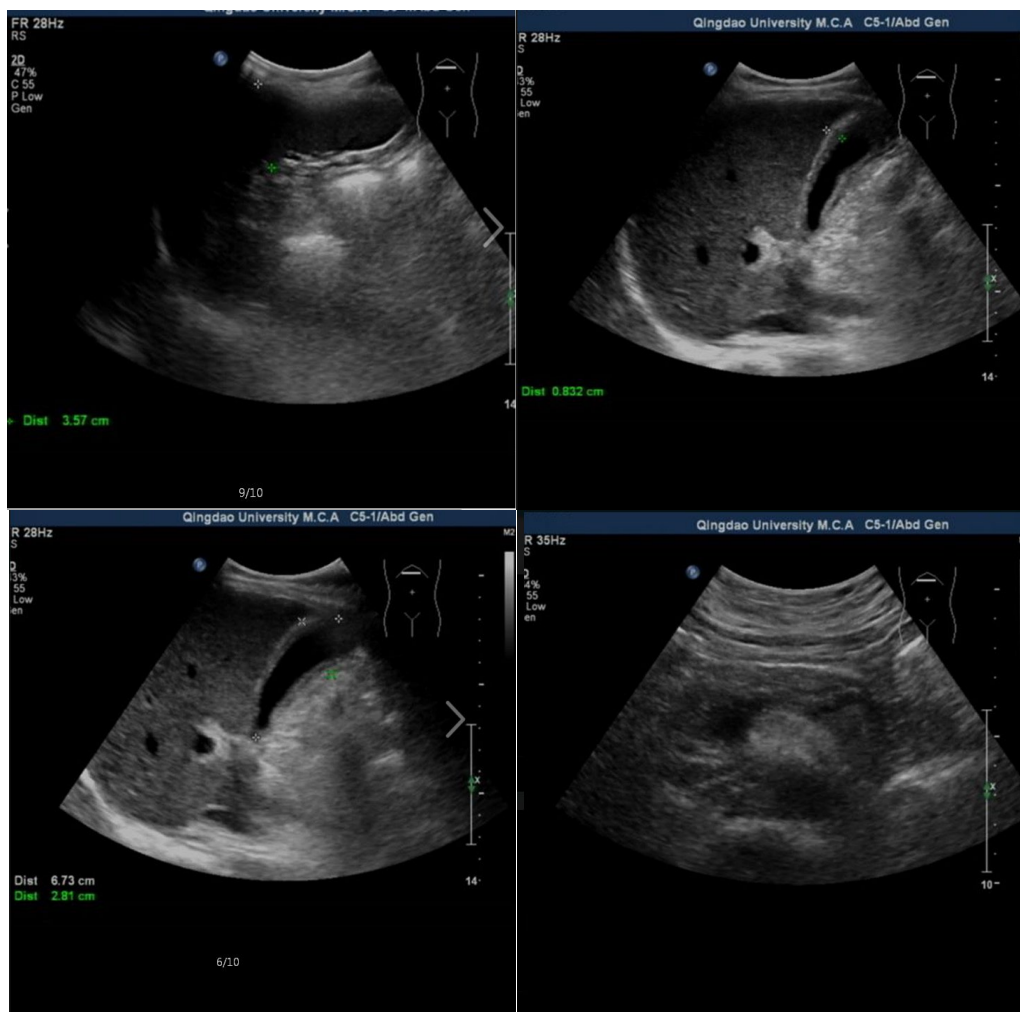
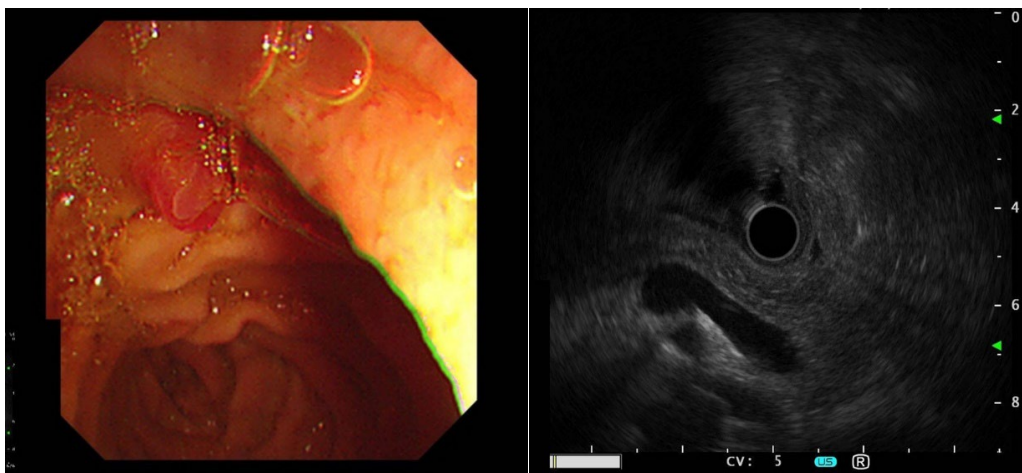


Figure 1. Abdominal ultrasound showing diffuse liver lesions

图 1. 腹部超声示肝脏弥漫性病变



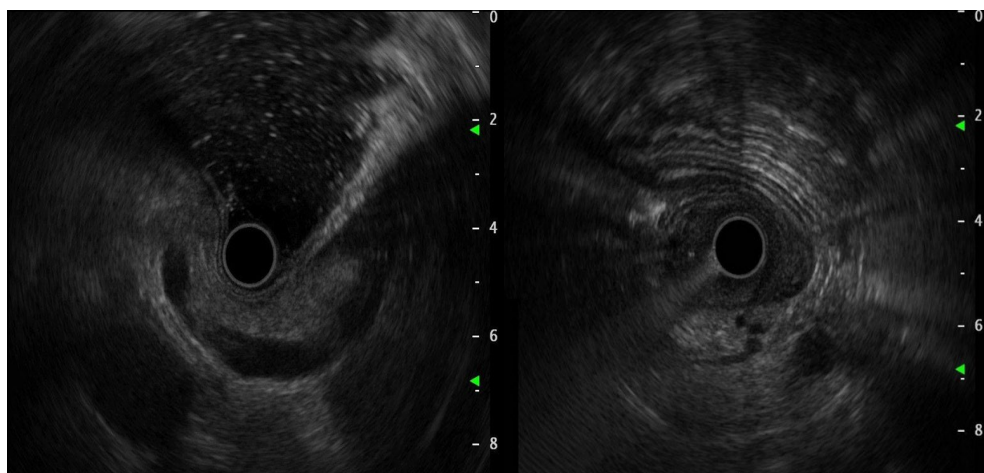


Figure 2. Ultrasound gastroscopy showing no dilatation of the common bile duct
图 2. 超声胃镜示胆总管无扩张

3. 讨论

3.1. 流行病学与临床特征

目前全球范围内报道的二甲双胍致 DILI 病例不足百例, 发生率 $< 0.1\%$ [10]。通过系统检索符合纳入标准的病例共 78 例, 其中女性占比 57.7%, 平均发病年龄 56.3 岁, 与本例患者(62 岁女性)特征基本一致。文献显示, 二甲双胍致 DILI 的潜伏期差异较大(1 周~2 年), 中位数为 45 天, 本例患者服药半月后出现肝功能异常, 符合典型潜伏期范围[11]。临床表型以肝细胞型损伤为主(占 72.1%), 表现为 ALT、AST 显著升高, 伴胆红素升高者占 58.9% [12], 与本例“转氨酶及胆红素同步升高”的特征吻合。

3.2. 机制研究进展

现有研究表明, 二甲双胍致 DILI 的机制存在明显个体差异, 主要涉及以下通路: 1) 线粒体功能障碍: 二甲双胍可特异性抑制肝脏线粒体呼吸链复合物 I, 导致 ATP 生成减少及活性氧(ROS)蓄积, 引发肝细胞凋亡[13], 本例肝穿刺可见“肝细胞弥漫性水肿、点状坏死”, 与线粒体损伤后能量代谢障碍直接相关——ATP 缺乏导致细胞膜钠钾泵功能受损, 水分渗入细胞引发水肿, 而 ROS 蓄积进一步加剧肝细胞坏死, 这与混合型偏肝细胞型损伤的病理基础一致。2) 乳酸代谢紊乱: 肝功能受损时乳酸代谢受阻, 可能形成“乳酸蓄积→肝细胞损伤→乳酸代谢进一步恶化”的恶性循环[14], 尤其在合并肾功能不全时风险更高。本例患者虽肾功能正常, 但胆红素持续升高(最高可达 $395.65 \text{ } \mu\text{mol/L}$)提示肝脏代谢功能严重受损, 可能间接抑制乳酸脱氢酶活性, 导致乳酸清除效率下降。尽管未检测血乳酸水平, 单黄疸加重与肝损伤进展的同步性, 支持乳酸代谢紊乱参与了损伤的持续放大。3) 免疫介导的特异质反应: HLA 基因型多态性(如 HLA-DRB1*15)可能与二甲双胍过敏反应相关[15], 本例患者治愈后再次使用口服降糖药(非二甲双胍)短期内即出现肝功能异常, 提示肝脏对药物存在高度敏感性, 这一“再激发”现象强烈支持特异质免疫机制的参与——即使未检测 HLA 基因型, 该临床表现也与文献中报道的 HLA 相关免疫介导损伤特征高度吻合, 凸显了个体免疫背景在二甲双胍肝毒性中的关键作用。通过系统回顾既往二甲双胍致 DILI 病例, 仅 5 例(6.4%)出现类似“再激发”现象, 但细究该 5 例特征可见明显差异: 其中 4 例为再次使用二甲双胍后复发, 且均表现为单纯肝细胞型损伤(R 值 5.2~7.8); 仅 1 例为更换其他降糖药(格列美脲)后出现肝功能异常, 但损伤类型为胆汁淤积型(R 值 1.8)。而本例为首次报道的“非同类药物再激发 + 混合型偏肝细胞型损伤”。这种独特的临床表型不仅丰富了二甲双胍相关特异质性肝损伤的谱系, 更提示部分

患者可能存在广谱药物敏感性,为临床用药选择(如本例最终需依赖胰岛素)提供了关键参考。该特征在既往文献中未见重复报道,进一步凸显了本例的罕见性及机制研究价值。

进一步结合本例混合型偏肝细胞型($R = 3.91$)的损伤模式分析:线粒体功能障碍主要导致肝细胞直接损伤(符合 ALT 显著升高),而免疫介导的炎症反应可能同时累及胆管上皮细胞,二者共同构成混合型损伤的病理基础。这一机制解析较单纯的讨论更贴合本例特征,也为“再激发”现象提供了合理的理论依据。

3.3. 诊断与鉴别诊断要点

RUCAM 评分是 DILI 诊断的金标准[16]。回顾既往报道,85%的二甲双胍致 DILI 病例 RUCAM 评分 ≥ 6 分,与本例 10 分(“极可能”)一致。根据国际共识,DILI 按 R 值分为肝细胞型($R \geq 5$)、胆汁淤积型($R \leq 2$)及混合型($2 < R < 5$) [17],分型对判断损伤机制及预后具有重要意义。本例患者 R 值 ≈ 3.91 ,属混合型偏肝细胞型,与文献报道的二甲双胍致 DILI 以肝细胞损伤为主的特征一致[18]。

鉴别诊断方面,需重点排除:1) 非酒精性脂肪肝:此类患者多伴代谢综合征,肝穿刺可见脂肪变性[19],与本例病理特征不符;2) 自身免疫性肝病:抗核抗体(ANA)、抗平滑肌抗体(SMA)阳性为典型表现[20],本例相关抗体阴性可排除;3) 胆道梗阻:MRCP 或超声胃镜可发现胆管扩张[21],本例影像学检查无相关证据。

3.4. 治疗与预后的文献总结

文献显示,二甲双胍致 DILI 的核心治疗为及时停药,90%的患者在停药后 4~8 周肝功能恢复正常[22]。保肝药物的选择中,甘草酸制剂(如天晴甘美)可通过抑制炎症因子改善肝细胞损伤[23],与本例治疗方案一致。预后方面,多数病例无长期肝损伤,但约 5%的患者可能出现药物敏感性增加[24],与本例“再次用药即复发”的特征吻合,提示此类患者需终身避免使用二甲双胍及结构相似的双胍类药物。

3.5. 本病例的特殊性与临床启示

二甲双胍作为双胍类口服降糖药,在 2 型糖尿病治疗中应用广泛且疗效显著。其主要作用机制是通过减少肝糖输出和增加外周组织对葡萄糖的利用,从而降低血糖水平[1]。二甲双胍的临床安全性普遍较高[2],尽管二甲双胍相关的胃肠道不适和代谢性酸中毒是该药广泛认可的副作用[25],但二甲双胍诱导的肝损伤的报道极少。随着二甲双胍处方量增加,其潜在肝毒性更加需要引起重视。

本病例中,患者长期服用二甲双胍且无其他肝毒性药物暴露史,却出现了严重肝功能损伤的表现,如黄疸、转氨酶显著升高和胆红素异常。停药后经对症治疗肝功能逐渐恢复,进一步证实二甲双胍与肝损伤的因果关系[10]。尽管二甲双胍致药物性肝损伤的发生率较低,但其潜在的危害性不容忽视。本例患者 R 值 ≈ 3.91 ,属混合型偏肝细胞型 DILI,提示损伤以肝细胞为主,这与肝穿刺活检所见的“肝细胞点状坏死”及文献报道的主要损伤类型一致,支持“二甲双胍主要直接损伤肝细胞而非胆管上皮细胞”的假设[26],为临床治疗中选择针对肝细胞修复的保肝药物(如谷胱甘肽)提供了依据。

基于上述机制与文献证据,临床医师使用二甲双胍时应注意:1) 患者筛选:治疗前,应详细评估患者的肝功能状态,避免在已有肝脏疾病或肝功能不全的患者中使用。2) 肝功能监测:治疗过程中定期监测患者肝功能指标,如 ALT、AST 及胆红素水平,以早期发现潜在的肝脏损伤。3) 患者教育:告知患者服药期间可能出现的不良反应,尤其是肝损伤早期症状(如黄疸、乏力、尿色加深等),以便及时就医[27]-[29]。

此外,本例患者治愈后再次出现药物性肝损伤,提示其肝脏对药物高度敏感[30]。该现象在临床上较

为罕见, 提示临床医师处理类似病例时, 需警惕患者肝脏对药物的敏感性变化, 避免再次使用可能引起肝损伤的药物。

本病例的报告为临床提供了宝贵的临床资料, 提醒临床医师使用二甲双胍时需保持高度警惕。本研究的局限性在于: 未明确患者服用二甲双胍的具体剂量及疗程; 未进行药物激发试验(因伦理风险), 无法完全确认二甲双胍的因果关系; 未检测 HLA 基因型等预测药物敏感性的指标。未来需要更多的研究进一步探讨二甲双胍致肝损伤的具体机制及风险因素, 优化用药策略, 降低不良反应发生率。综上, 二甲双胍虽为 2 型糖尿病治疗的有效药物, 但其潜在的罕见肝毒性应引起重视。通过合理筛选患者、定期监测肝功能及加强患者教育, 可以在很大程度上预防和早期识别药物性肝损伤, 保障患者用药安全。

声 明

该病例报道已获得病人的知情同意。

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