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CASE REPORT

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Mutant *TP53* driving the Warburg Effect in Mantle Cell lymphoma

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Abstract

The p53 mutation R273H in tumor cells leads to increased glucose uptake, lactic acidosis, and accelerated tumor growth, as was previously shown in mice. We here present a patient with mantle cell lymphoma harboring this p53_R273H mutation, whose clinical course is characterized by severe lactic acidosis, hypoglycemia, and aggressive disease.

KEYWORDS

lactic acidosis, mantle cell lymphoma, P53, p53_R273H mutation, warburg effect

1 | INTRODUCTION

Metabolic changes are a hallmark of cancer.[1] Lactate overproduction by tumor cells in oxidative environment (aerobic glycolysis) is known as the Warburg effect.[2,3] The cancer biology of using this inefficient way of producing energy is under investigation.[4,5] Lactic acidosis (blood pH <7.35, lactate >4.0 mmoL/L)[6,7] results from tissue hypoxia during severe conditions like shock or hypoperfusion, hepatic failure, or drugs blocking oxidative phosphorylation.[8] Lactic acidosis attributed to aerobic glycolysis has been reported from individual patients in many different types of cancer (Table 1).[9–14] The mechanism of cancer-associated lactic acidosis is unknown.

Lactic acidosis in cancer is possibly associated with *TP53* gene mutations.[6] One of the most prevalent *TP53* mutation in cancer is R273H (Arg273His), which is found in the general population with an allele frequency of 0.0016% (NCBI database). Recent preclinical work established a direct link between oncogenic driver mutations, aerobic glycolysis, and lactic acidosis. In a murine model,[5] introduction of the p53 pathogenic mutation R273H in tumor cells (p53_R273H) resulted in a gain of function in the expression of glucose receptors and glucose uptake. Simultaneously, the negative regulation of wild-type p53 on glycolysis was lost, causing severe lactic acidosis and accelerated tumor growth, which was sensitive to inhibition of glycolysis. This suggested that p53_R273H may induce lactic acidosis and aggressive tumor growth in cancer patients, and that mutant p53-induced glycolysis might be a target in p53_R273H-mutated tumors. Clinical evidence supporting the validity of this mechanism is lacking.

We report a patient with mantle cell lymphoma and severe lactic acidosis, where targeted sequencing of potential oncogenic drivers revealed two mutations in the *TP53* gene, including p53_R273H. To our knowledge, this is the first lymphoma patient case where we establish a direct

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link between lactic acidosis and the oncogenic mutation R273H in the clinical setting, supporting the role of this mutation in the pathogenesis of tumor-associated lactic acidosis.

2 | CASE PRESENTATION

The 68-year-old non-diabetic patient presented weight loss, sweats, tachypnea, and lymphadenopathy. Personal history was remarkable for a cured renal cell carcinoma and a chronic hepatitis B, which was not under treatment at the time of diagnosis. Family history was significant for a "bone marrow tumor" in the maternal family. Peripheral blood showed lymphocytosis (absolute lymphoid count (ALC) 11×10^9/l, 53% abnormal lymphoid cells, LDH 5.6 ukat/l (ULN <4.42 ukat/l)), and lactic acidosis (lactate 10.6 mmoL/L, pH 7.31, pCO2 4.1 kPa, anion gap 20.4 mmoL/L). Bone marrow and lymph node biopsies revealed blastoid mantle cell lymphoma (MCL; 40% proliferation) overexpressing cyclin D1, SOX11, and p53 in stage IV B disease with high-risk MIPI-score of 7.5.

NGS mutational profiling (Oncomine® Myeloid Research Assay, 40 oncogenic driver genes, 30 fusion transcripts) revealed two p53 mutations, p.R273H (*TP53* c.818G > A), SNV, 19% allele frequency, potentially pathogenic, and p.K319Ter (*TP53* c.955A > T), SNV, 19% frequency, pathogenic. The K319Ter mutation in known from several tumors, including Non-Hodgkin lymphoma, and results in nonsense substitution in the protein tetramerization region with a p53 allele functional loss.

Under initial immunochemotherapy (Rituximab, Dexamethasone, high dose AraC, Oxaliplatin), lactate levels decreased in line with tumor response (ALC 0.6 ×10^9/l, LDH normal, lactate 7.5 mmoL/L). Due to poor patient tolerance, therapy was resumed using R-CHOP with ensuing response (ALC 0.4 ×10^9/l, no lymphoid/blast) and improvement of the patient's condition. The patient thereafter declined therapy continuation. He returned 2 months later with progressive splenomegaly and leukocytosis (ALC 40×10^9/l, 40% lymphoid cells, LDH 5.57 ukat/l, lactate not done), and second line treatment with Ibrutinib and Bortezomib was initiated. Therapy initially resulted in an improvement of peripheral blood (ALC 1.9 ×10^9/l, 3% lymphoid cells, LDH normalized), but the disease progressed after 4 months (ALC 21×10^9/l, 53% lymphoid cells, LDH 6.17 ukat/l, lactate 13.0 mmoL/L, transfusion-dependent thrombocytopenia). Bone marrow histology showed subtotal infiltration by blastoid lymphocytes. Salvage immunochemotherapy (Cytarabine, Rituximab) resulted in ALC 1.6 ×10^9/l (7% lymphoid cells), but no change in thrombocytopenia or lactate (12.7 mmoL/L) and renal failure AKI 3 (increased potassium, hyperphosphatemia, hyperuricemia), with subsequently aggravated lactic acidosis (lactate 14.6 mmoL/L, pH 7.16). Despite of an improvement of renal function after rehydration and sodium bicarbonate, serum lactate levels continued to rise (maximum 18.0 mmoL/L), in parallel with increased lymphoid cell counts (ALC 22×10^9/l, 21% lymphoid cells, LDH 8.92 ukat/l). The patient refused further systemic therapy, was transferred to outpatient palliative care, and deceased at home. Flowchart of patient history from the time of MCL diagnosis is presented in Figure S1.

3 | DISCUSSION

Significant lactic acidosis was present in this patient initially, improved with treatment response and worsened as the disease progressed. The patient hyperventilated throughout the course of disease (respiratory rates up to 30/min, hypocapnia), suggesting a partial respiratory compensation of metabolic acidosis. Recurrent hypoglycemia (minimal blood glucose 2.3 mmoL/L, adequately suppressed insulin/C peptide) was observed with disease progression. Adrenocortical insufficiency, hepatic failure, and drug-induced acidosis were ruled out. There were no signs of tissue hypoperfusion or vascular causes for hyperlactatemia. We interpreted this lactic acidosis as the result of excessive aerobic glycolysis by aggressive mantle cell lymphoma due to the Warburg effect, possibly in conjunction with p53 mutations.

The p53-protein is strongly involved in the regulation of glucose uptake. A lack of p53 leads to increased glucose uptake through dysregulated activity of glucose transporters GLUT1, GLUT3, and GLUT4.[15–17] Because p53 regulates TIGAR (TP53-induced glycolysis and apoptosis regulator) as well as phosphofructokinase (PFK), the rate-determining enzyme of glycolysis, the loss of p53 results in increased glucose utilization and excessive pyruvate production.[18,19] Through binding to glucose-6-phosphate dehydrogenase (G-6-PD), the rate-limiting enzyme of the

TABLE 1 Different types of cancer linked with the Warburg effect in the past

Leukemia[9]
Aggressive diffuse large B-Cell Lymphoma[9]
Glioblastoma[9,10]
Colorectal cancer[11]
Breast cancer[12]
Lung cancer[12]
Prostate cancer[13]
Gynecologic cancers (ovarian, endometrial, cervical cancer)[14]

pentose phosphate pathway (PPP), wild-type p53 (wtp53) suppresses active G-6-PD formation. The loss of this inhibitory effect leads to an elevated metabolization of glucose in the PPP, thereby increasing nucleic acid biosynthesis and supporting cell proliferation.[20] Through activation of phosphatase and tensin homolog kinase (PTEN), wtp53 indirectly suppresses phosphatidylinositol 3-kinase (PI3K), leading to decreased production of v-akt murine thymoma viral oncogene homolog (AKT) and hypoxia inducible factor (HIF). Cells with a loss of p53 function lack the inhibiting effect on these enzymes, leading to an increased glycolysis and decreased oxidative phosphorylation.[15,18] HIF activates lactate dehydrogenase (LDH), increasing lactate production.[21] Therefore, as depicted in Figure 1, the loss of active p53 in cancer cells results in increased glucose uptake, aerobic glycolysis, and lactate production and is consistent with the murine model.[5]

When screening frequently mutated tumor-driving genetic regions in this patient's tumor tissue, only two *TP53* mutations were detected; this suggests that the observed effects may be attributed to p53 with reasonable confidence. Mutant p53 exerts a dominant negative effect by preventing wtp53 from binding to the promoter of its target genes, so that active wtp53 function is lacking in this patient's lymphoma. The R273H missense mutation results in expression of full-length mutant p53 (p53_R273H) protein, consistent with the strong p53 expression observed by immunohistochemistry. p53_R273H is lacking the tumor-suppressive functions of wtp53. Instead, it has gained new oncogenic functions independent of wtp53

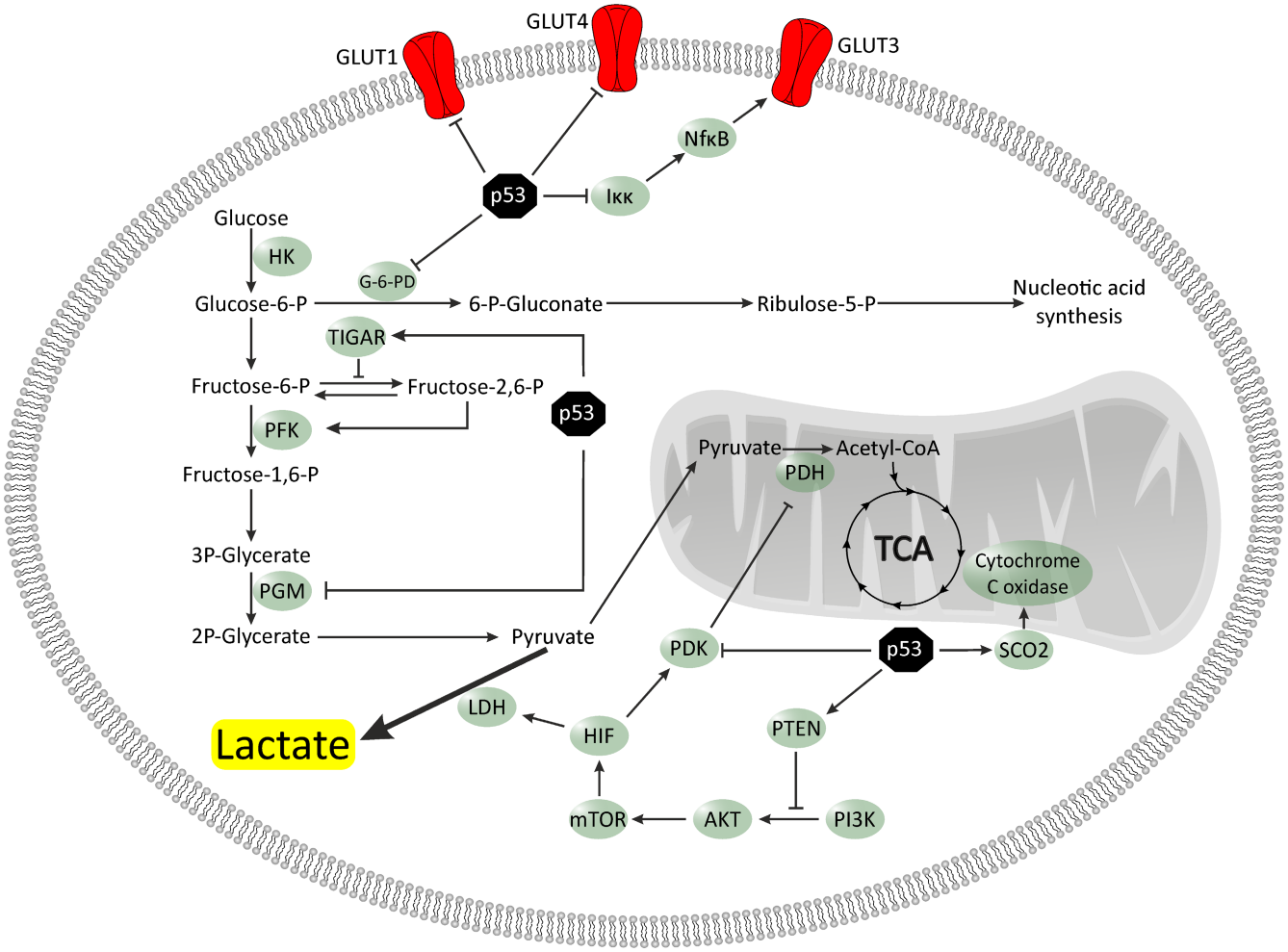

FIGURE 1 Schematic picture of the mechanism by which p53 influences cellular glucose metabolism. AKT, v-akt murine thymoma viral oncogene homolog; G-6-PD, Glucose-6-phosphate dehydrogenase; GLUT, Glucose Transporter; HIF, hypoxia inducible factor; HK, Hexokinase; IKK, Ikappaβ kinase; LDH, lactate dehydrogenase; mTOR, mechanistic target of rapamycin; NFKβ, nuclear factor kappa β; PDH, pyruvate dehydrogenase; PDK, pyruvate dehydrogenase kinase; PFK, phosphofructokinase; PGM, phosphoglycerate mutase; PI3K, phosphatidylinositol 3-kinase; PTEN, phosphatase and tensin homolog kinase; SCO2, synthesis of cytochrome C oxidase 2; TCA, tricarboxylic acid cycle; TIGAR, Tp53-induced glycolysis and apoptosis regulator.

and actively stimulates the Warburg effect in cancer cells, leading to considerably higher levels of glucose uptake, glycolytic rate, and lactate production, compared with wtp53 or p53 −/−.[5]

4 | CONCLUSION

We conclude that in this patient with aggressive mantle cell lymphoma, lactic acidosis was associated with the loss of wtp53 combined with acquisition of p53_R273H. This is the first direct evidence to support that R273H mutated p53 drives lactic acidosis in cancer patients in the clinical setting. Our case study sustains the validity of preclinical models and points to the glucose metabolism as a therapeutic target in selected p53-mutated tumors.

AUTHOR CONTRIBUTIONS

JK collected the data, designed, and performed the research and wrote the original manuscript. AB wrote the manuscript and designed the figure. KKS and MS proofread the manuscript and interpreted the data and conclusions. CD contributed to both writing and editing the manuscript. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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