

## Recurrent Hypoglycemia And Hypothermia in A Patient With Hodgkin's Disease

A 60-year-old woman presented to her primary care physician with fatigue and anemia. Laboratory evaluation revealed a hemoglobin level of 9.8 g/dL and an erythrocyte sedimentation rate (ESR) of 64 mm/hour. She subsequently developed nocturnal episodes of diaphoresis, confusion, and hypothermia. Capillary glucose measurements during the spells revealed hypoglycemia. During two supervised fasts, the patient's plasma glucose levels fell to 35 mg/dL and 32 mg/dL, respectively. Plasma insulin and C-peptide levels were appropriately suppressed, but a low concentration of  $\beta$ -hydroxybutyrate and normal increase of plasma glucose concentration after a glucagon injection suggested the presence of an insulin-like substance. Computed tomographic (CT) scan of the abdomen and subsequent positron emission tomographic (PET) scan revealed extensive lymphadenopathy. Biopsy of periaortic lymph nodes revealed Hodgkin's disease of the mixed cellularity type. Following chemotherapy, a complete remission ensued, the spells abated, and hypoglycemia was not induced by a 23-hour fast. We believe that the patient's Hodgkin's disease was producing an insulin-like substance. The observations of others suggest that this substance may be an autoantibody to the insulin receptor.

Haematologica 2006; 91(10):e137-e138

Hypoglycemia<sup>1-8</sup> and hypothermia<sup>9</sup> have been previously reported in association with Hodgkin's disease, but the mechanisms of these disorders have not been clarified. In this report, we describe a woman with Hodgkin's disease, severe neuroglycopenia, and hypothermia, whose hypoglycemia was probably related to the production of an insulin-like substance and whose hypothermia was secondary to the hypoglycemia.

### Case Report

A previously healthy 60-year-old woman was referred to the Hematology/Oncology Section of the Gundersen Lutheran Medical Center for evaluation of a microcytic anemia. Physical examination was normal. Complete blood count revealed the following: White blood count, 5100 K/ $\mu$ L with 71% neutrophils, 18.7% lymphocytes, 4.3% monocytes, 3.1% eosinophils, and 2.9% basophils. Hemoglobin was 9.8 g/dL, hematocrit 30.5%, and red blood cell count 4.14 M/ $\mu$ L. The mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration were 73.7 fL, 23.6 pg, and 32 g/dL, respectively. Serum iron was 13  $\mu$ g/dL (normal range, 20-160) and total iron binding capacity 228  $\mu$ g/dL (normal range, 200-400). The percent saturation was 5.7% (normal range 12-50). Ferritin level was 91 ng/mL (normal range, 20-228). Serum and urine protein electrophoresis, quantitative serum immunoglobulin measurements, and total serum kappa and lambda light chain measurements provided either normal or borderline non-specific changes. Serum immunofixation studies showed that all fractions were polyclonal. Bone marrow aspirate and biopsy did not reveal a malignancy.

The patient developed nocturnal episodes of diaphoresis and confusion associated with hypothermia. Hypoglycemia associated with hypothermia was docu-

Table 1. Table Results of Laboratory Studies During Two Supervised Fasts.

Laboratory Study	Reference Range	Patient Value	
		First Fast	Second Fast
Plasma glucose	60-100 mg/dL	35	32
Insulin (fasting)	1.4-14 $\mu$ U/mL	1.1	<0.1
C-peptide	170-900 pmol/L	<33	<33
Proinsulin	3-20 pmol/L	7.1	
$\beta$ -hydroxybutyrate	<0.4 mmol/L	0.5	
Cortisol	7-23 $\mu$ g/dL	20	
Growth hormone	0-10 ng/mL	8.1	
IGF-1	71-290 ng/mL		56
IGF-2	230-970 ng/mL		438
IGFBP3	0.9-3.7 mg/L		1.5
Insulin Antibodies	<3%		<3%

Figure 1. Representative glucose and corresponding temperature values.

mented with a home blood glucose meter (Figure 1). Ten hours and 40 minutes after starting a supervised fast, the patient's plasma glucose fell to 35 mg/dL. At this time, we measured insulin, glucoregulatory hormones and pertinent laboratory parameters (Table 1) and injected glucagon intramuscularly. Forty minutes later, her plasma glucose level peaked at 102 mg/dL.

Thirty-nine days later, we performed another fast. The patient's plasma glucose level fell to 32 mg/dL after 10 hours at which time insulin and C-peptide levels were again appropriately suppressed. Insulin-like growth factor 1 (IGF-1) was slightly low but insulin-like growth factor 2 (IGF-2), insulin growth-factor binding protein 3 (IGFBP-3), and insulin antibody levels were normal (Table).

We obtained a computed tomographic (CT) scan of the upper abdomen to exclude an insulinoma. Although the pancreas was unremarkable, the CT scan showed lymphadenopathy in the retrogastric, periaortic, and pericaval regions, and splenomegaly. CT of the chest revealed extensive cervical, supraclavicular, and mediastinal lymphadenopathy. CT-guided biopsies of the periaortic lymph nodes and neck mass showed mixed cellularity Hodgkin's disease. Positron emission tomographic (PET) scan performed for staging purposes revealed extensive tracer uptake in multiple regions corresponding to the lymphadenopathy noted on CT scan.

The patient was given a stage assignment of IIIA and was started on doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) chemotherapy. One month after the first chemotherapy cycle, the patient's hypoglycemic

spells abated. The patient received a total of 6 cycles of ABVD chemotherapy over a 6-month period. One month after completing chemotherapy, the PET scan revealed no evidence of active Hodgkin's disease; 16 months after completing chemotherapy, the extensive lymphadenopathy and splenomegaly could not be detected by CT scanning. The patient has remained well and free of spells 5 years after completion of treatment, at which time her glucose remained normal (95 mg/dL) after a 23-hour fast.

### Discussion

Our patient developed severe fasting hypoglycemia before the diagnosis of Hodgkin's disease was clinically apparent. Low plasma insulin and C-peptide levels excluded insulin as the hypoglycemic agent. A glucose response following the administration of glucagon >25 mg/dL and a relatively low  $\beta$ -hydroxybutyrate value (<2.7 mmol/L) after fasting, however, are consistent with the presence of an insulin-like substance.<sup>8</sup> The level of one such substance, IGF-2, was normal. Hypoglycemia in patients with Hodgkin's disease has been previously reported.<sup>1-8</sup> Cachexia,<sup>1</sup> extensive liver infiltration,<sup>2</sup> insulin secretion by pancreatic islet cells stimulated by adjacent Hodgkin's tumors,<sup>3</sup> and production of a poorly characterized insulin-like substance by malignant cells<sup>4</sup> have been suggested as possible causes of the hypoglycemia. Braund *et al.* reported on a 76-year-old man with Hodgkin's disease and fasting hypoglycemia who displayed impaired *in vitro* binding of insulin to erythrocyte insulin receptors.<sup>5</sup> The patient's plasma immunoglobulin fraction inhibited binding of insulin to normal donor erythrocytes. The patient's hypoglycemia remitted and insulin binding became normal after prednisolone therapy.<sup>5</sup> Walters and coworkers described a patient with Hodgkin's disease who had severe fasting hypoglycemia.<sup>6</sup> Her serum contained a factor found in the immunoglobulin fraction that stimulated glucose uptake by rat adipocytes. The substance also displaced insulin bound to human erythrocytes and precipitated and phosphorylated human insulin receptors. Chan reported on a 49-year-old Chinese man with Hodgkin's disease, hypoglycemic attacks, and suppressed plasma insulin levels.<sup>7</sup> The authors demonstrated reduced binding of insulin to insulin receptors that were exposed to the patient's plasma.<sup>7</sup> The patient's hypoglycemic attacks were abolished after 4 weeks of prednisone therapy. The authors of these three reports postulate that patients with Hodgkin's disease can produce autoantibodies to the insulin receptor, resulting in insulin-like effects and hypoglycemia.<sup>5-7</sup>

Hypothermia associated with Hodgkin's disease has been reported previously in 12 patients.<sup>9</sup> The cause of hypothermia in such patients remains unknown. Hypoglycemia causes peripheral vasodilatation, sweating, and inhibits shivering, commonly resulting in hypothermia.<sup>10</sup> We believe that hypoglycemia rather than a direct effect of Hodgkin's disease was the cause of hypothermia in our patient.

### Conclusion

In summary, we describe a patient with Hodgkin's disease who experienced recurrent episodes of hypoglycemia and hypothermia that abated with chemotherapy-induced remission. The association of low levels of plasma insulin and C-peptide with evidence for insulin action suggest the presence of an insulin-like substance. The association of autoimmune phenomena in Hodgkin's disease such as hemolytic anemia, thrombocytopenia, and erythema nodosum, and the work of others suggest but do not prove that this factor is an autoantibody to the insulin receptor.<sup>5-8</sup>

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Keywords: Hodgkin's, hypoglycemia, hypothermia

Acknowledgements: This case report was supported by a grant from the Gundersen Lutheran Medical Foundation. The authors thank Cathy Fischer and Angela Kuhn for expert assistance with manuscript preparation  
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