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## Hypoglycemia in a Patient With a Big “Big”-IGF-II-Producing Tumor

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**N**on-islet cell tumor-induced hypoglycemia is a rare cause of hypoglycemia (1). Mesenchymal and epithelial tumors account for most cases (2, 3). A 60-year-old man with a palpable abdominal mass (computed tomography scan, 12 × 16 × 16-cm lesion, retroperitoneal) presented with neuroglycopenia responding to iv glucose. A fasting test confirmed symptomatic hypoglycemia (plasma glucose, 2.3 mmol/L within 4 h). Plasma levels of insulin (0.2 mU/L) and C-peptide (<10 pmol/L) were suppressed, excluding endogenous hyperinsulinemia. Plasma IGF-I was also suppressed (<2.6 nmol/L). Plasma total IGF-II was normal (460 ng/mL; +0.57 SD score) but pro-IGF-IIIE (68–88) (“big”-IGF-II) was markedly raised (98 ng/mL; +8.97 SD score) (4). In agreement with the hypothesis that aberrant processing of IGF-II disrupts the ternary complex of IGF-II, IGF-binding protein 3, and acid labile subunit, we show here that pro-IGF-IIIE (68–88) was mainly present within binary complexes and as plasma free “big”-IGF-II (Figure 1). This would increase its accessibility to insulin and IGF-I receptors, ultimately leading to hypoglycemia and suppression of the pituitary GH-IGF-I axis (2, 3). Our patient fully recovered after surgery (histology, Figure 2), and successfully passed a 72-hour fasting test (glucose, 4.6 mmol/L). All laboratory parameters, including pro-IGF-IIIE (68–88), had normalized. The distribution of “big”-IGF-II in the postoperative plasma became comparable to control plasma (Figure 1). The patient is still asymptomatic 1 year after surgery, with 10-year recurrence-free survival expected to be 50% (5). “Big”-IGF-II-producing tumors should be considered in

tumor patients presenting with hypoglycemia. This case demonstrates that the ensuing changes in “big”-IGF-II distribution toward free pro-IGF-IIIE (68–88) coincide with IGF-I suppression and are fully reversible.

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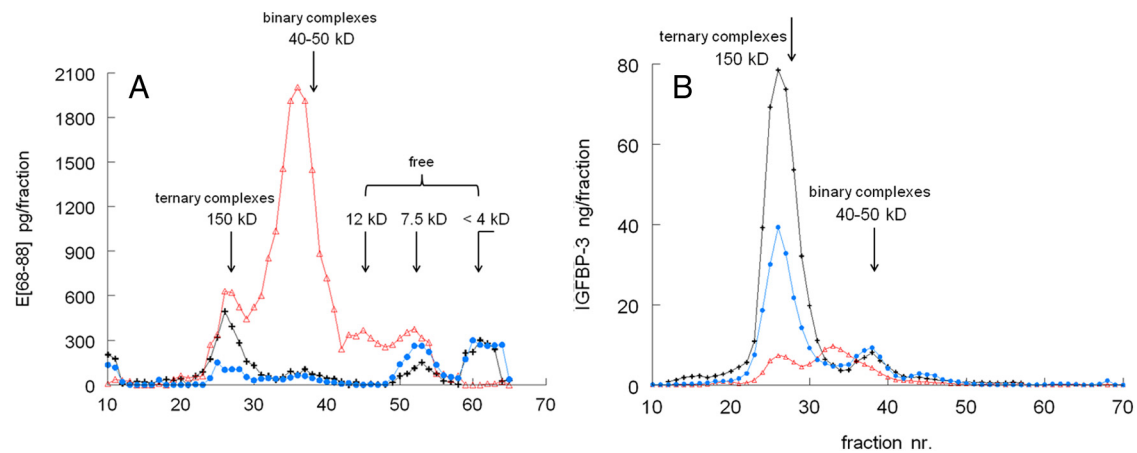
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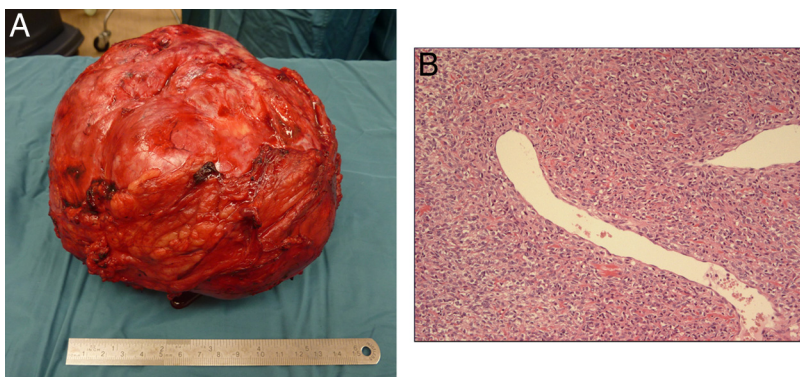
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**Figure 1.** A, Column chromatography of "big"-IGF-II, demonstrating a marked concentration of pro-IGF-II (68–88) immunoreactivity in binary complexes (~40–70 kDa) and free "big"-IGF-II (~12 kDa) at the expense of ternary complex (~150 kDa) before surgery ( $\Delta$ , red) (<7.5 kDa, free E (68–88) containing fragments). These abnormalities normalized after surgery ( $\bullet$ , blue), now comparable to control plasma (+, black). B, Reduced preoperative levels of IGF binding protein 3 (IGFBP-3), contributing to further reduction of ternary (and binary) complexes. The equal distribution of IGFBP-3 between these complexes before surgery, as opposed to after surgery and control distribution, underscores the interference of "big"-IGF-II with the formation of 150-kDa complexes.



**Figure 2.** A, Macroscopy of the tumor that was located in the abdominal cavity and retroperitoneum and was removed in total ( $19 \times 19 \times 12$  cm; weight, 1.76 kg). B, Histopathological examination revealed a typical pattern of a solitary fibrous tumor without unfavorable features of necrosis or high mitotic activity.