SUN-101

Background: Achondroplasia (ACH) is the most common non-lethal skeletal dysplasia. Fibroblast growth factor receptor 3 (FGFR3) plays a crucial role in bone elongation, demonstrated by FGFR3 gain-of-function mutations in individuals with ACH and hypochondroplasia. Multiple therapeutic strategies have been considered for ACH, the most advanced is to employ an analog of C-type Natriuretic Peptide (CNP), which antagonizes the MAP kinase (MAPK) pathway. Here, we evaluated a therapeutic strategy that targets all pathways downstream of FGFR3 (e.g., STAT1), not just MAPK. We hypothesized that a very low dose of the oral selective FGFR1-3 tyrosine kinase inhibitor (TKI) infigratinib (BGJ398) would be able to improve defective bone elongation. We also hypothesized that infigratinib would have greater potency at lower concentrations in an ACH cell line than a CNP analog (e.g., vosoritide) given its effects on multiple downstream pathways. **Methods:** A mouse model (*Fgfr3*$^{Y367C/+}$) mimicking ACH was treated with subcutaneous injections of infigratinib daily (0.2 or 0.5 mg/kg/day) or intermittently (1 mg/kg, every 3 days) for a treatment duration of 15 days (PND1-15). *In vivo* results were compared with vehicle-treated mutant mice. TAN 4-18-chondrocytes, a human chondrocyte line expressing a heterozygous Y373C *FGFR3* mutation, were treated with multiple concentrations of infigratinib and vosoritide and MAPK levels were measured. **Results:** We observed a significant improvement of the upper (humerus +7%, ulna +11%) and lower (femur +11%, tibia +16%) limbs at 0.5 mg/kg/day, and improvement in the foramen magnum. The effect of infigratinib on bone elongation was reduced with a lower dose (0.2 mg/kg), confirming a dose-response relationship. With intermittent injections of infigratinib (1 mg/kg, every 3 days), gain of growth was significant for all the long bones (+7%) and the size of the foramen magnum was increased. Modification of the growth plate structure, displaying better organization, was also seen. In cell line data, compared with FGF18-treated TAN 4-18-chondrocytes, concentrations of 10^{-6}M to 10^{-10}M infigratinib led to statistically significant ($p<0.05$) improvements. With vosoritide treatment, a concentration of 10^{-4}M led to statistically significant improvements compared with FGF18-treated chondrocytes ($p<0.05$), although this was not seen at 10^{-5}M. **Conclusions:** Preclinical ACH mouse model data indicate that low, as well as intermittent, doses of infigratinib promote growth and can improve the foramen magnum. No apparent toxicity of infigratinib was observed, suggesting that TKI therapy has the potential to be a valuable and relevant option for children with ACH. Furthermore, cell line data indicate that infigratinib showed superior potency over a CNP analog, suggesting that inhibition of multiple FGFR3-related pathways vs MAPK inhibition alone may lead to increased efficacy.

Tumor Biology

ENDOCRINE NEOPLASIA CASE REPORTS I

Case Report: Malignant Pheochromocytoma

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SUN-939

Case Report: Malignant Pheochromocytoma

Introduction: The concept of malignancy for pheochromocytoma is complex and the best definition is the presence of metastases, according to WHO. Anatomopathological scoring systems are not effective in predicting metastases. Malignancy should be considered when tumors larger than 8cm (> 80g), paragangliomas (especially retroperitoneal), dopamine / methoxythyramine increase, Ki67> 6% and SDHB mutation. At 5 years, survival ranges from 50-69%. Metastases may appear 20-40 years after initial treatment of pheochromocytoma. We describe a case that metastasis was identified 33 years after pheochromocytoma excision

Case report: A 57-year-old female patient with a postoperative history of 33 years of right adrenal pheochromocytoma was discharged from the endocrinologist after 10 years of follow-up. At diagnosis 33 years ago, she had symptoms of hypertension with paroxysms and weight loss that disappeared after tumor removal. 2 years investigating weight loss with general practitioner without another celebratory. On physical examination, orthostatic hypotension was highlighted. Plasma methanephrine 0.8 nmol / L (VR <0.5) and plasma normetanephrine 1.8 nmol / L (VR <0.9), chromogranin A 5.7 nmol / L (VR <3 nmol / L) and clonidine test with 36.6% suppression of metanephrines, suggesting tumor recurrence. MRI localized recurrence of the adrenals and MIBG scintigraphy with I^{131} that showed, respectively, in the topography next to the paracaval and retroportal right diaphragmatic crura, isointense T1 and slightly hyperintense T2 at 1.8 cm and radiopharmaceutical hypercaptation in right adrenal topography. Genetic panel by NGS did not identify germline mutation in 22 pheochromocytoma-related genes. FDG PETCT was consistent with MRI and MIBG images. Gallium $PETCT^{68}$ DOTATOC detected the lesions already described, in addition to a lytic lesion in the left femoral intertrochanteric medulla. Anatomopathological approached abdominal lesion confirming pheochromocytoma metastasis in lymph node conglomerate. Currently has a negative methanephrine plasma, however chromogranin A 142 ng / mL (VR <93), and was chosen by the observant approach.

Conclusion: The case of the patient illustrates that pheochromocytoma should be followed indefinitely, as metastases may appear many years later and may present different aggressiveness potentials.

Bone and Mineral Metabolism

BONE AND MINERAL CASE REPORTS I

Ga-DOTATATE and Tumor Induced Osteomalacia: Finding the Culprit Lesion

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SAT-337

Introduction

Tumor-induced osteomalacia (TIO) is a very rare paraneoplastic disorder caused by tumors that produce fibroblast growth factor 23 (FGF23) resulting in phosphate

wasting and inadequate bone mineralization. Complete resection can be curative; however, these tumors are typically difficult to identify due to size and location.

Clinical case

A 43-year-old man was referred to Endocrinology for evaluation of recurrent fractures and hypophosphatemia. First stress fracture was diagnosed at age 41, followed by musculoskeletal pain in several locations. Lower extremity MRI showed chronic left fibular stress fracture, new stress fracture in fifth metatarsal and right tibia. Tc99m-MDP bone scan revealed multiple foci of increased tracer uptake in bilateral ribs, hips, and lower extremities. Laboratory evaluation showed normal calcium (9.3 mg/dL, normal range [NR]: 8.7-10.2), low phosphorus (1.5 mg/dL, NR: 2.5-4.7), low 1,25-dihydroxyvitamin D (13 pg/mL, NR: 19.9-79.3), low 24-hour urine calcium (78mg), high phosphate excretion fraction in urine (27%, normal <5%), high ALP (163 U/L, NR: 38-126), and high FGF23 (238 RU/mL, NR<180). 25 OH vitamin D (36 ng/mL) and iPTH (5.7 pmol/L, NR: 1.6-6.9) were normal. Patient was started on calcitriol and phosphate supplements. Due to concern for TIO, a PET scan with 68Ga-DOTATATE was performed which showed multiple somatostatin avid lesions concerning for metastatic disease. However, after re-review with radiology, it was felt that other areas of uptake were due to fractures and not tumor given remarkably higher SUV in left acetabular lesion (SUV 20 vs 4-5). The left acetabular lesion was biopsied, followed by surgical resection. Pathology was consistent with phosphaturic mesenchymal tumor with uninvolved margins. FGF23 normalized within 24 hours after surgery (127 RU/mL) and calcitriol and phosphate supplements were discontinued on post-operative day 10.

Clinical lesson

TIO is a rare paraneoplastic syndrome commonly caused by phosphaturic mesenchymal tumors that secrete FGF23. Once the diagnosis of TIO is confirmed, the tumor is localized by anatomical or functional imaging. 68Ga-DOTATATE scan is currently the imaging modality of choice for localization. However, there are other pathologic processes, such as fractures, that could affect the interpretation of PET scans. Osteoblastic activity is increased in fractures, which results in increased uptake in Ga-DOTATATE PET scan since osteoblasts express somatostatin receptor. Our patient was initially thought to have multiple avid lesions concerning for metastatic disease, but culprit lesion was differentiated based on SUVs and confirmed with biopsy. Clinical and biochemical abnormalities resolved after surgery. Early recognition of culprit lesion in TIO is crucial, as successful surgery is curative and would lead to significant improvement in the quality of life of patients.

Cardiovascular Endocrinology

HYPERTRIGLYCERIDEMIA; INFLAMMATION AND MUSCLE METABOLISM IN OBESITY AND WEIGHT LOSS II

Immunologic Effects of GLP-1 Activation in Obese Adipose Tissue

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SUN-544

Background: Obesity is associated with systemic inflammation which is thought to stem, in part, from adipose tissue (AT). Obese AT is characterized by infiltration of pro-inflammatory T cells that promote macrophage activation and inflammation. GLP-1 has been shown to have anti-inflammatory effects in previous studies. We hypothesized that promotion of GLP-1 signaling with liraglutide or sitagliptin would reduce inflammation in association with an increase in the number of anti-inflammatory invariant natural killer T cells (iNKTs), group 2 innate lymphoid cell (ILC2s) and regulatory T cells (Treg) in blood and AT.

Methods: Obese adults with pre-diabetes were randomized to pharmacologic treatment resulting in increased GLP-1 signaling (liraglutide or sitagliptin, N=8), or hypocaloric diet (N=3). This ongoing study is blinded, so the effects of liraglutide and sitagliptin are combined in analyses and referred to as "drug". Subcutaneous abdominal AT and peripheral blood mononuclear cells (PBMCs) were collected at baseline ("pre") and after 12 weeks of therapy ("post"). Phenotypic marker expression of blood and AT T cells were characterized by flow cytometry. Whole AT inflammatory gene expression in the pre and post groups was assessed by Nanostring.

Results: Using the Nanostring inflammation panel, we found that a number of pro-inflammatory genes were significantly downregulated in whole AT after treatment with drug, including CD163, CD86, CCR1, MCP-2, and MCP-4. Blood ILC2s were significantly decreased with drug treatment (pre 3.95%±3.05, post 1.71% ±1.65, p=0.01), but not diet (pre 2.17% ±1.91, post 1.46% ±1.68, p=0.18). We did not detect a change in Treg numbers after treatment with either diet (pre 5.78% ±1.91, post 6.09% ±1.50, p=0.29) or drug (pre 6.49% ±2.29, post 5.94% ±2.15, p=0.12). Similarly, no difference in blood iNKT numbers was detected after diet (pre 0.063% ±0.044, post 0.082% ±0.049, p=0.11) or drug (pre 0.077% ±0.106, post 0.091% ±0.130, p=0.67).

As observed in the PBMCs, adipose ILC2s were decreased after drug (pre 2.04% ±1.67, post 1.32% ±1.58, p=0.07, N=4). We did not detect a change in AT Treg and iNKT numbers (Treg pre 9.24% ±5.36, post 6.23% ±1.55, p=0.14; iNKT pre 0.12% ±0.08, post 0.09% ±0.05, p=0.47, N=4).

Conclusions: In a small pilot study of obese pre-diabetic patients treated with drugs that activate GLP-1 signaling (liraglutide or sitagliptin) or hypocaloric diet, global transcriptional analysis of whole AT suggested decreased inflammation with drug therapy. However, we found decreased percentages of ILC2 cells (considered anti-inflammatory in adipose) in both blood and AT after drug treatment. Future experiments will further characterize the function of these cell types, and evaluate other immune subsets in PBMC and AT that may be responsible for decreasing inflammation.

Adrenal

ADRENAL - CORTISOL EXCESS AND DEFICIENCIES

Clinical Features of Immune Checkpoint Inhibitor-Related Adrenal Insufficiency: A Retrospective Analysis

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