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Tocilizumab for the treatment of paraneoplastic inflammatory syndrome associated with angiomatoid fibrous histiocytoma

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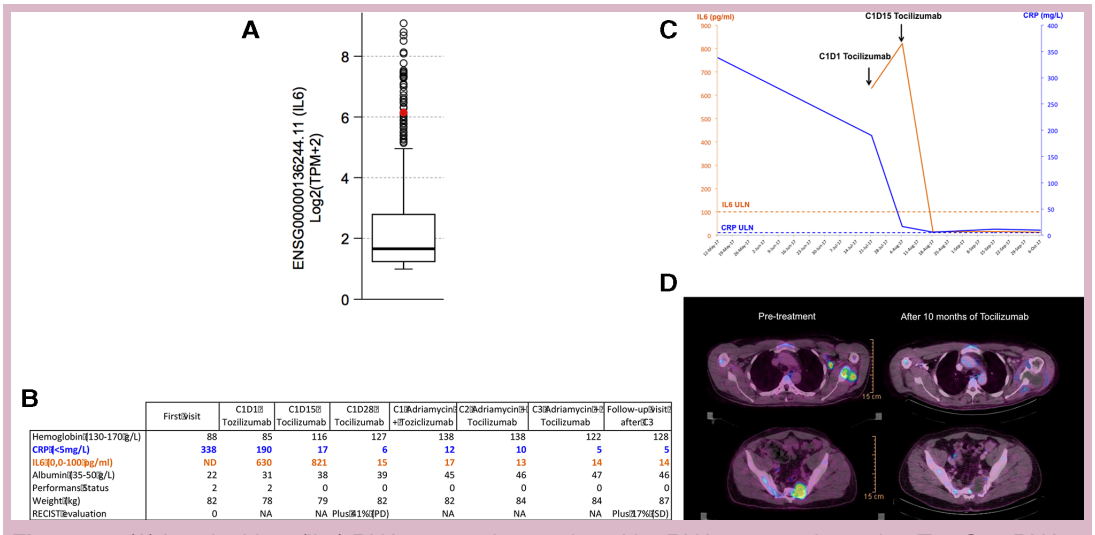
Angiomatoid fibrous histiocytoma (AFH) is a rare sarcoma affecting children and young adults, with rare (1%) metastatic recurrence[1] and driven by different gene fusions (*EWSR1-ATF1*, *FUS-ATF1* and *EWSR1-CREB1*, the latter being the most common).[2] Paraneoplastic inflammatory syndrome (PIS) is frequently associated with AFH: the *EWSR1-CREB1* translocation involves *CREB1*, a transcription factor which binds to the interleukin 6 (IL6) promoter region.[3] Whether the *EWSR1-ATF* transcript can activate the IL6 gene similarly is unknown.

We report the case of a 53-year-old male patient with bone and lymph node recurrence of an AFH of the left thigh, 18 months after surgery of the primary tumour. He presented with an 8-month history of left sciatica, fatigue, weight loss, fever and severe cough. RNA sequencing confirmed the *EWSR1-ATF1* translocation and high expression of IL6 mRNA (figure 1A). C reactive protein (CRP) was 338 mg/L, and plasmatic IL6 more than six times the upper limit value (figure 1B,C).

Based on the previous experience with a non-humanised anti-IL6 antibody, a treatment with the anti-IL6 monoclonal antibody, tocilizumab (8 mg/kg/2 weeks for 1 month, then every 3 weeks) provided a spectacular improvement of symptoms: after only two infusions, fever and cough completely regressed, CRP and IL6 normalised (figure 1B,C). The PET-scan evaluation after three infusions



First visit	C1D1 Tocilizumab	C1D15 Tocilizumab	C1D28 Tocilizumab	C1 Adriamycin + Toziclizumab	C2 Adriamycin Tocilizumab	C3 Adriamycin Tocilizumab	Follow-up visit after C3
Hemoglobin (130-170 g/L)	88	85	116	127	138	138	122	128
CRP (<5mg/L)	338	190	17	6	12	10	5	5
IL6 (0,0-100 pg/ml)	ND	630	821	15	17	13	14	14
Albumin (35-50 g/L)	22	31	38	39	45	46	47	46
Performans Status	2	2	0	0	0	0	0	0
Weight (kg)	82	78	79	82	82	84	84	87
RECIST evaluation	0	NA	NA	Plus 81% (PD)	NA	NA	NA	Plus 17% (SD)

Figure 1 (A) Interleukin 6 (IL6) RNA expression analysed by RNA sequencing using TrueSeq RNA Access Library Prep Kit (IlluminaVR). The boxplot represents IL6 expression from 1062 sarcoma samples. Our case (represented as the red dot) is among the 65 highest IL6-expressing tumours (open circle). (B,C) Evolution of clinical, biological and radiological parameters. (D) PET-CT scan before tocilizumab and after 10 months of treatment, showing a near complete metabolic response, but radiological progression. CRP, C reactive protein; NA, Not Applicable; ND, Not Dosed; PD, progressive disease, PET, Positron Emission Tomography; RECIST, Response Evaluation Criteria in Solid Tumor; SD, stable disease, ULN, upper limit of normal.

showed a complete metabolic response (figure 1D) but morphological progression, required additional systemic therapy. Adriamycin, pazopanib, ifosfamide and trabectedin were given sequentially, in combination with tocilizumab, yielding a progression-free survival of 2, 9, 2, and 1 month, respectively. The patient eventually died from a bacterial infection 24 months after the initiation of tocilizumab, in a context of disease progression.

The impact of anti-IL6 on AFH growth remains unclear. This patient had a complete metabolic response on PET (maximal SUV (standardized uptake value) from 7.6 to 3.2) but a morphological progression (+38%). The role of IL6 as a growth factor in this case is unclear: IL6 was reported to act as an intracrine growth factor in renal cell carcinoma, preventing anti-IL6 antibody to inhibit the signal.[4]

Treatment with tocilizumab was overall well tolerated, though a contribution to the lethal infection cannot be excluded, as reported in patients with rheumatoid arthritis. Interestingly, while the patient had disease progression despite 4 lines of therapy, overall survival was 24 months, beyond what is reported for advanced sarcoma with inflammatory syndrome and primary progression to doxorubicin. Long-term control of PIS more than a direct antineoplastic effect of tocilizumab possibly contributed to the 24-month survival. A partial metabolic response and remission of IL6-induced PIS with tocilizumab was previously reported in a case of a paediatric metastatic AFH with an *EWS-CREB1* fusion.[5]

Treatment with tocilizumab led to remission of severe IL6-induced PIS associated with metastatic AFH, where IL6 overproduction is likely related to the oncogenic fusion involving transcription factors regulating IL6. The contribution of this anti-IL6 antibody to clinical tumour growth factor in AFH remains to be established, and will be further explored.

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