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When Decades of Classical Work-up Fail in Chronic Brucellosis: Understanding Disease Trajectory Through Complete HLA Haplotype Analysis

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Abstract

A 59-year-old man presented a more than twenty-year trajectory after exposure-related febrile illness (2005), inflammatory osteoarticular disease, PCR-documented osteoarticular brucellosis (2019) with negative serology, IgAκ monoclonal gammopathy, and an incomplete SAPHO label. Despite repeated imaging, broad negative infectious and autoimmune testing, and successive antibiotics, methotrexate, TNF/IL-17 inhibitors, and pamidronate, no durable clinical or biological improvement was obtained; late MRI/PET suggested inactive sequelar bone disease, while systemic inflammation and disability persisted. After ischemic stroke with patent foramen ovale (2026), complete HLA typing was interpreted with digitHLA expert tool. Beyond a B8–Cw1–DR4 triad, HLA-B18 framed neuroectodermal–mesenchymal involvement shaped by molecular mimicry and epigenetic indexing after Brucella triggering—read as neurogenic para-osteoarthropathy (POAN) rather than active SAPHO—and suggested individualized therapeutic orientations beyond further undifferentiated immunosuppression. This case argues that detailed HLA haplotype analysis can clarify chronic post-brucellar trajectories when classical pathways stall.

Keywords: brucellosis; HLA haplotype; digitHLA; HLA-B18; POAN; neurogenic para-osteoarthropathy; chronic inflammation; SAPHO; monoclonal gammopathy; personalized medicine; case report

Introduction

Brucellosis may evolve from acute infection to focal osteoarticular disease and prolonged symptomatic states in which culture, serology, and even imaging become discordant [1-4]. In such patients, clinical practice often cycles through infectious, rheumatologic (including SAPHO), and hematologic hypotheses, multiplying tests and immunosuppressive trials without restoring function [5]. Human leukocyte antigen (HLA) polymorphism influences susceptibility and phenotype in several infection-triggered and dysimmune disorders, including osteoarticular brucellosis, although reported associations vary by population [6]. Beyond single-allele associations, complete haplotype reading-crossing class I/II alleles with exposure history and clinical trajectory-may better explain polymorphic, treatment-refractory courses [8]. We report a two-decade case in which an exhaustive classical pathway failed to improve the patient, whereas detailed HLA haplotype analysis provided a coherent narrative of disease unfolding and candidate therapeutic directions (Figures 1-3; Tables 1-2).

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Classical pathway: long course, extensive testing, limited benefit

A 59-year-old Caucasian man was reassessed in 2026 for chronic inflammation, multifocal osteitis history, documented brucellosis, and IgAκ monoclonal gammopathy (Figure 1; Table 1).

Figure 1. Classical pathway timeline versus persistent disability (2005-2026)

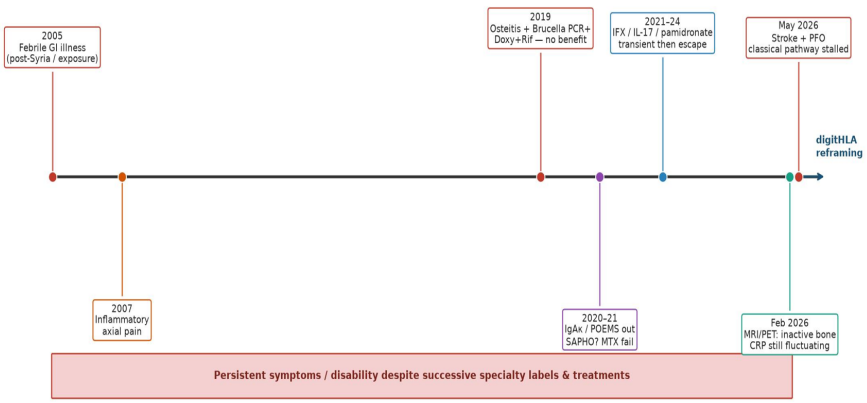


Figure 1: Timeline of the classical pathway (tests and treatments) versus persistent disability (2005–2026). Despite successive infectious, rheumatologic, hematologic, and later neurovascular labels, no durable clinical remission was achieved until haplotype-level reframing with digitHLA.

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TABLE 1: *CLASSICAL WORK-UP: EXHAUSTIVE NEGATIVES AND THERAPEUTIC NON-RESPONSES.*

Domain	Finding / intervention	Result for patient care
Microbiology (2019)	Iliac-wing biopsy PCR for Brucella	Positive; serology negative
Antibiotics (2019)	Doxycycline + rifampin, 3.5–4 months	Poorly tolerated; no clinical / biological / radiological improvement; no post-Rx PCR control
Hematology	IgAκ monoclonal peak ≈3.5 g/L; myelogram ≈5% plasma cells; VEGF; EMG	POEMS excluded; MGUS-like component persisted
Rheumatology label	Incomplete SAPHO (no cutaneous features)	Historically "probable"; late MRI/PET without active osteitis
Immunosuppression	Methotrexate 25 mg/week × 6–8 months	No meaningful clinical gain
Biologics	Infliximab; secukinumab (± dose escalation); ixekizumab	Transient IL-17 response then escape; overall failure to control disease
Bone-directed	Pamidronate 90 mg × 3 monthly infusions	Insufficient benefit
Autoimmunity / genetics	HLA-B27; TRAPS; ANA; ANCA; anti-CCP	All negative / non-contributory
Differential infection	QuantiFERON; Whipple PCR; Rickettsia; Coxiella; fungi; S. aureus on biopsy	Negative
Myeloid genetics	NGS myeloid panel; KIT D816V	Negative / absent
Organ safety labs	Renal function, calcium, liver tests	Preserved
Late imaging (2026)	MRI bone edema; PET-CT metabolic activity	No active osteitis; sequelar osteocondensation
Neurology / cardio (2026)	Left occipital ischemic stroke; TEE	PFO ≈9×4 mm; closure planned — does not explain 20-year osteoarticular course
Net outcome	Specialty silos over >20 years	No durable remission; no unifying host model until HLA haplotype analysis

2005. After travel to Syria, severe febrile gastroenteritis with night sweats lasted ≈6 months. He reported Maghreb travel and contact with horses and soil.

2007. Inflammatory dorsalgia with morning stiffness spread to pelvis and spine.

2019. Multifocal pain (scapular, sternal, spinal, sacroiliac, knees, ankles) with high CRP (often 56–130 mg/L; peak 224 mg/L). Imaging: multifocal osteocondensing lesions (sternum, sternoclavicular joints, vertebrae, sacrum, iliac wings). Right iliac-wing biopsy: chronic osteitis; *Brucella* PCR positive; serology negative. Doxycycline + rifampin for 3.5–4 months was poorly tolerated and produced no clinical, biological, or radiological improvement; no post-treatment microbiological control.

2020–2021. IgAκ monoclonal peak; POEMS excluded (normal VEGF; EMG without polyneuropathy; myelogram ≈5% non-dystrophic plasma cells). Incomplete SAPHO proposed (no acne, pustulosis, psoriasis, nail disease, uveitis, or frank peripheral synovitis). Methotrexate 25 mg/week × 6–8 months: no meaningful gain.

2021–2024. Infliximab ineffective. Secukinumab brought transient improvement (CRP 9 mg/L, Dec 2022) then escape despite dose escalation; ixekizumab failed; secukinumab resumed. Pain migrated to pelvis/lower limbs; fatigue worsened. Pamidronate 90 mg × 3 monthly infusions: insufficient benefit. Tramadol (up to 400 mg/day for ~5 years) was tapered off by Oct 2025. Intravenous iron twice for refractory iron deficiency.

February 2026. February 2026. Rheumatology: historically "very probable" SAPHO without active osteitis (no MRI bone edema; sequelar osteocondensation; PET-CT without significant metabolic activity; no suspicious visceral/vascular focus)—yet symptoms and fluctuating CRP continued. Imaging therefore argued against an active SAPHO/CNO process and left the long osteoarticular phenotype without a unifying label.

15 May 2026. Left occipital ischemic stroke with transient complete aphasia; no major cardiovascular risk factors. TEE: PFO ≈9 × 4 mm (closure planned Jan 2027).

September 2026 status. Major asthenia, cognitive fog, post-exertional pain flares, fluctuating axial/lower-limb pain, intermittent right-hand electric shocks, fluctuating medial thigh swelling; no fever, frank synovitis, or typical SAPHO skin disease. CRP still 10–80 mg/L; IgAκ ≈3.5 g/L.

Bottom line of the classical pathway: infection documented once (tissue PCR), then years of sophisticated differentials and potent therapies without durable improvement or a unifying host model (Table 1).

HLA haplotype analysis: reframing the trajectory

Extended HLA typing retained: A1, A9, B8, B18, Cw1, Cw7, DR4, DR8, DQ3, DQ4 (input alleles included A1, A24, B8, B18, Cw1, Cw7, DR8, DR11, DQ3, DQ4). Analysis was performed with digitHLA, a haplotype-centered expert-system / decision-support tool that helps analyze comorbidities associated with HLA haplotypes [8]. The method is described in a white paper deposited on HAL [8] and presented by the developer company at https://hla-expert.com/.

digitHLA synthesis emphasized a **B8–Cw1–DR4 triad** (Figure 2):

Allele focus	Interpretive contribution in this case
HLA-B18	After Brucella infection, neuroectodermal and mesenchymal targeting shaped by molecular mimicry and epigenetic indexing; digitHLA clinical synthesis toward neurogenic para-osteoarthropathy (POAN)
HLA-B8	Mesenchymal / neuro-ectodermal crossroads; psoriatic-leaning dysimmune terrain; pathways toward chronic osteoarticular and myopathic-type phenotypes
HLA-Cw1	Axial skeletal profile (sacroiliitis / Forestier-like / SpA-adjacent patterning), matching the patient's axial–pelvic dominance
HLA-DR4	Predisposition to seronegative chronic polyarthritis-like evolution and dysgammaglobulinemic risk—congruent with IgAκ without myeloma criteria

Figure 2. digitHLA haplotype summary — retained alleles and B8-Cw1-DR4 triad

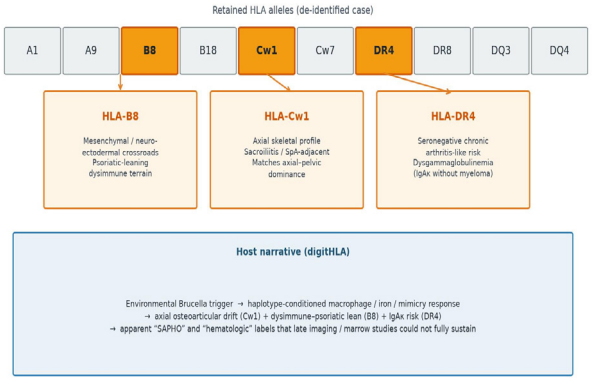


Figure 2: *digitHLA haplotype summary — retained alleles and B8–Cw1–DR4 triad (de-identified). The triad links axial osteoarticular drift (Cw1), dysimmune–psoriatic lean (B8), and dysgammaglobulinemia risk (DR4) into a single host narrative after Brucella triggering.*

Composite indices ranked high for psoriatic, dysimmune, celiac-leaning, xenobiotic/porphyric, and tuberculin-related epigenetic loadings, with comparatively lower cardiovascular/ neurodegenerative and tumor/hemopathy indices (Figure 3). The software's clinical reading was that the osteoarticular "SAPHO-like" label and the monoclonal IgAκ drift are host expressions of the same haplotype-shaped response to a *Brucella* (and macrophage/iron-related) trigger—not proof of ongoing culture-positive infection, and not adequately addressed by undifferentiated immunosuppression.

In summary, digitHLA linked the post-brucellar course—neuroectodermal and mesenchymal involvement under HLA-B18, reactivity of molecular mimicries, and epigenetic indexing—to a complex phenotype corresponding to the evolution of a neurogenic para-osteoarthropathy (POAN). Importantly, digitHLA was used not to re-prove Brucella persistence, but to ask whether the exceptional duration and polymorphism of disease map onto an objectifiable immunogenetic configuration—and they did.

Therapeutic avenues suggested by the haplotype reading

From the digitHLA orientation module, individualized directions were proposed as hypothesis-generating, to be supervised clinically (Table 2). In the table, only active principles are listed and numbered; commercial preparation names appear in the key beneath the table.

A. Mechanistic axes

1. Host iron homeostasis — limit iron availability exploitable in Brucella/macrophage persistence; address martial dysregulation beyond simple repletion (link to ferroptosis / Fenton chemistry as framed in the report).
2. Reduce fibrotic / post-tuberculin epigenetic drive — mycobacterial desensitization; antifibrotic support.
3. Xenobiotic / porphyric load — review porphyrinogenic drug cascades amplified by successive classical regimens; detoxification / chelation.
4. Dysimmune tolerance (HLA-G) — alleles A1, DR4, DQ4 flagged for HLA-G–related approaches [9].
5. Local immune irritants — periodontal / occlusal rehabilitation; removal of dental irritative foci and intraoral metals.
6. Nutritional and physical rehabilitation as baseline companions.

B. Numbered active principles and preparations (Table 2)

See Table 2 for the numbered active principles proposed by digitHLA, with the corresponding commercial / named preparations listed in the key beneath the table.

These items are outputs of the haplotype analysis, not claimed here as established standard of care. Selection, dosing, interactions, and monitoring remain the responsibility of the treating physicians.

The clinical claim of this report is specific: after classical medicine exhausted its labels and drugs, haplotype analysis changed the explanatory model and the therapeutic search space.

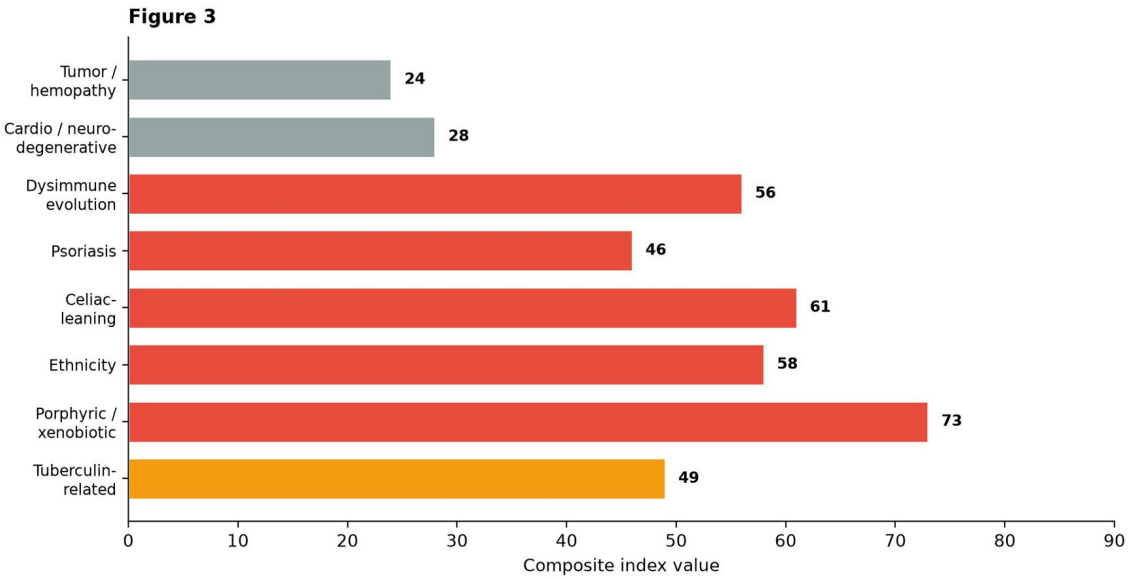


Figure 3*: digitHLA composite index loadings (de-identified case). Higher values correspond to psoriasis, dysimmune, celiac-leaning, xenobiotic/porphyric and tuberculin-related axes; lower values correspond to cardio-neurodegenerative and tumor/hemopathy axes.*

Table 2:*Therapeutic avenues derived from digitHLA haplotype analysis* — NUMBERED ACTIVE PRINCIPLES (HYPOTHESIS-GENERATING).*

No.	Domain	Active principle
1	Redox / ferroptosis regulation	Synthetic peroxidases
2	Gene-expression regulation	Plant-alkaloid–based gene-regulation complexes
3	Pain adjunct (same axis as 2)	Plant-alkaloid–based gene-regulation complexes
4	Iron / ferritin regulation	Raubasine
5	Gene-expression lock	Alstonine
6	Immune tolerance (HLA-G)	HLA-G protein [9]
7	Tuberculinism / fibrosis	Mycobacterium chelonae antigen (homeopathic desensitization)
8	Tuberculinism / fibrosis	Mycobacterium antigen (homeopathic desensitization)
9	Tuberculinism / fibrosis	β-Sitosterol
10	Tuberculinism / fibrosis	*Ginkgo biloba* extract (Autumn golden leaf)
11	Brucella-specific	Brucella antigen (Korsakovian desensitization)
12	Porphyric / xenobiotic state	Pao phytocomplex + raubasine + alstonine
13	Detoxification / chelation	Heme-metabolite detoxification complex
14	Biotope rehabilitation	Bacteriophages
15	Antimicrobial (spirochetes)	Cryptolepis sanguinolenta
16	Antimicrobial (vibrios / H. pylori)	Sulforaphane
17	Cross-cutting support	Nutritional rehabilitation measures
18	Cross-cutting support	Neuro-occlusal / stomatologic rehabilitation (non-pharmacological)
19	Antiviral adjunct (report note)	Ivermectin
20	Antiviral adjunct (report note)	Fenbendazole

**These items are outputs of the haplotype analysis, not claimed here as established standard of care. Selection, dosing, interactions, and monitoring remain the responsibility of the treating physicians*.

Discussion

This case is presented less as “another chronic brucellosis” than as a failure analysis of the classical pathway and a demonstration of haplotype-level reasoning (Figures 1–3).

For twenty years the patient accumulated legitimate but fragmented diagnoses: zoonotic exposure, PCR-proven osteitis, seronegative discordance, MGUS-like IgAκ, incomplete SAPHO, stroke–PFO. Each fragment triggered appropriate specialty tests; none produced sustained remission (Table 1). That pattern is precisely when a host map becomes medically useful.

Complete HLA reading with digitHLA reframed the story as: environmental intracellular trigger (Brucella), HLA-B18–conditioned neuroectodermal–mesenchymal response shaped by molecular mimicry and epigenetic indexing, axial osteoarticular drift (Cw1) + dysimmune–psoriatic lean (B8) + dysgammaglobulinemia risk (DR4) induce a POAN (neurogenic para-osteoarthropathy) trajectory rather than sustained active SAPHO/CNO, with “hematologic” labels that imaging and marrow studies could not fully sustain (Figure 2).

Therapeutic implication: stop cycling through broader immunosuppression by default; instead pursue haplotype-guided, mechanism-proximal levers summarized in Table 2, while keeping the door open to targeted microbiological re-evaluation if a new focal sample is justified.

Limitations

• Single case; digitHLA outputs are decision-support, not a substitute for controlled trials. No peer-reviewed methods paper on digitHLA is available yet; the tool is documented in a white paper [8], also presented at https://hla-expert.com/.

• Species-level Brucella identification and post-antibiotic PCR follow-up were incomplete historically.

• Stroke is adequately explained by PFO and should not be over-attributed to brucellosis without specific neurovascular evidence.

• Proposed therapies require prospective clinical validation and safety monitoring.

Conclusion

Decades of classical investigation and treatment in this PCR-documented osteoarticular brucellosis case did not restore health or unify the phenotype. Detailed HLA haplotype analysis (HLA-B18–centered POAN reading within a B8–Cw1–DR4 digitHLA profile) supplied that missing host narrative and redirected care toward individualized therapeutic avenues. We suggest that complete haplotype interpretation deserves a formal place when long post-infectious inflammatory trajectories remain refractory to specialty silos.

Preparation key (commercial / named preparations corresponding to Table 2 numbers)

(1) TIB DH8 and TIB DH9 (Laboratoire Kimicor, Italy)
(2) MT40, MT41 and MT33 (Laboratoire Kkena, Italy)
(3) MT31 and MT32 (Laboratoire Kkena), on demand for pain
(4) MT41
(5) MT41
(6) Fertilized quail eggs (OCF) [9]
(7) Mycobacterium chelonae 8D (Pharmacie Hildegarde, Brussels, Belgium)
(8) Mycobacterium D4
(9) β-Sitosterol
(10) Ginkgo biloba (Autumn golden leaf)
(11) Korsakovian homeopathic desensitization on Brucella
(12) Phytotherapeutic association MT42 (=MT40 + MT41)

(13) HMF (Hémofénix)
(14) Bacteriophage preparations
(15) Cryptolepis sanguinolenta TM
(16) Sulforaphane
(17) Nutritional rehabilitation program such as KrissLaure
(18) Planas-type neuro-occlusal rehabilitation (NRO); exclusion of dental irritative foci; elimination of intraoral metals; physical therapy
(19) Ivermectin
(20) Fenbendazole

Author contributions

T. Nawrocki analyzed the case with digitHLA. M. Jarretou compiled the complete clinical history. C. Touzet and T. Nawrocki developed digitHLA. C. Touzet is the corresponding author / guarantor.

Conflicts of interest / Competing interests

C. Touzet and T. Nawrocki developed the digitHLA software. Access to digitHLA is free of charge through a non-profit association. T. Nawrocki formulates the food supplements of Kkena SRL.

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Patient consent

Written informed consent was obtained from the patient for publication of this anonymized case report and any accompanying de-identified images/tables. A copy of the written consent is available for review by the Editor-in-Chief of this journal upon request.

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Cursor, an AI platform, was used to put the manuscript into form and to help with the figures.

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