SUPPLEMENTAL INFORMATION

Accuracy of Generative Artificial Intelligence Models in Differential Diagnoses of Familial Mediterranean Fever and Deficiency of Interleukin-1 Receptor Antagonist

Joshua Pillai*, Kathryn Pillai

*Correspondence should be addressed to J.P. (joshpillai949@gmail.com)

This PDF includes:

All 40 patient vignettes given in the same randomized order as the artificial intelligence models. This will aid in comparing future models with the published patient vignettes. Patients numbered 1-20 are DIRA patients and 21-40 are FMF patients.

Clinical Vignette 8
Age: 5 day-old. **Sex:** Male. **Clinical Presentation:** The patient presented with mouth ulcers, pustular dermatitis, severe pustulosis, and pathergy. The patient was previously treated with antibiotics, antiviral and antifungal agents, ibuprofen, methylprednisolone sodium succinate, and prednisolone. **Related Family and Patient History:** The patient is from Lebanon but currently living in Sweden. Parents were Consanguineous. The patient's birthweight was 3220 g. **Physical Examination:** Radiography showed skeletal abnormalities. The patient had widening of ribs, periosteal elevation, and Conjunctival injection. **Laboratory Results:** None.
Reference Paper: Aksentijevich, I., Masters, S. L., Ferguson, P. J., Dancey, P., Frenkel, J., Van Royen-Kerkhoff, A., Laxer, R. M., Tedgård, U., Cowen, E. W., Pham, T., Booty, M. G., Estes, J. D., Sandler, N. G., Plass, N., Stone, D. L., Turner, M. L., Hill, S., Butman, J. A., Schneider, R., . . . Goldbach-Mansky, R. (2009). An Autoinflammatory Disease with Deficiency of the Interleukin-1–Receptor Antagonist. *The New England Journal of Medicine*, *360*(23), 2426–2437. https://doi.org/10.1056/nejmoa0807865

Clinical Vignette 16

Age: 2 week-old.
Sex: Male.
Clinical Presentation: The patient initially presented with cutaneous eruption on his neck and antecubitals that evolved into erythematous pustular plaques covering most of the surface area of his body. At 6 months, hospitalization occurred for femur osteomyelitis along with lytic lesions on the vault and right femur.
Related Family and Patient History: The patient was of Puerto Rican descent and was born with congenital hip dysplasia. Consanguinity is unknown to the patient's parents.
Physical Examination: The patient had diffuse erythematous scaly plaques with overlying pustules involving 80% body surface area and digital anonychia. Lesional skin revealed psoriasiform dermatitis with subcorneal neutrophilic pustules. Radiography showed bowing of the long bones, broadened ribs, distal metaphyseal enlargement, and osteopenia. CT scan showed no pulmonary fibrosis.
Laboratory Results: Skin bacterial culture was normal. Laboratory evaluations were remarkable for chronic leukocytosis, microcytic anemia, thrombocytosis, and an elevated erythrocyte sedimentation rate (58 mm/h).

Reference Paper: Brau-Javier, C. N., Gonzales-Chavez, J., & Toro, J. R. (2012). Chronic cutaneous pustulosis due to a 175-kb deletion on chromosome 2q13. *Archives of Dermatology*, *148*(3), 301. https://doi.org/10.1001/archdermatol.2011.2857

Clinical Vignette 35

Age: 3.5 year-old.
Sex: Female.
Clinical Presentation: The patient presented with musculoskeletal pain, particularly knee pain, and recurrent pain crises consisting of sudden, severe, generalized abdominal pain and fever lasting 12 - 16 h.
Related Family and Patient History: The patient's ethnicity is East-European and North African-Arab descent. The patient has faced the same symptoms since the age of 6 months-old, every 1 - 2 months and lasting 16 - 24 h. However, they have been increasing frequency and progressed to weekly episodes. The patient is a carrier of beta-thalassemia trait but has no other significant medical or surgical history. The mother reported that the patient developed reactions including difficulty breathing to dimethindene, cetirizine, cefuroxime, and amoxicillin/clavulanate. Her mother is a carrier for beta-thalassemia trait. Her father has no known medical conditions. Her parents do not have any relative genetic predispositions.
Physical Examination: None.
Laboratory Results: Erythrocyte sedimentation rate (52 mm/h), blood leukocytes (17,100/μL), C-reactive protein (185 mg/L), hemoglobin (9.7 g/dL), platelet (376,000/mm3). Urinalysis was positive for ketones.

Reference: Darwish, W. M., Darwish, S., Darwish, M., & Darwish, B. F. (2021). M680I/M694V heterozygous mutation in early onset familial Mediterranean fever. *Journal of Medical Cases*, *12*(9), 351–354. https://doi.org/10.14740/jmc3747

Clinical Vignette 24

Age: 71 day-old.
Sex: Male
Clinical Presentation: The patient presented with complaints of fever.
Related Family and Patient History: The patient's ethnicity is not known. He was previously treated for neonatal sepsis due to fever with no focus at another medical center at 22 days-old. He had an 11 year-old sister with Familial Mediterranean fever. Ceftriaxone was started intravenously in possibility of occult bacteremia and complications of late neonatal sepsis. He was discharged after 72 hours, with 48 hours free of fever. The patient returned again with complaints of fever, and was discharged again. However, the patient returned again after 15 days with a fever.
Physical Examination: Examination showed no focus or abnormalities of the fever.
Laboratory Results: During his first admission his white blood cells (22300/mm3), hemoglobin (10.4 g/dL), thrombocytes (457000/mm3), C-reactive protein (39.3 mg/L). During the patient's third admission, white blood cells (17200/mm3), hemoglobin (9.03 g/dL), thrombocytes (520000/mm3), C-reactive protein (208 mg/L), and serum amyloid A (949 mg/L).

Reference: Kübra, A., Sarici, S. U., Kolukisa, G., & Altun, D. (2020). Familial Mediterranean Fever with Neonatal Onset: Case Report. *Case Reports in Pediatrics*, *2020*, 1–3. https://doi.org/10.1155/2020/6649525

Clinical Vignette 38

Age: 48 year-old.
Sex: Women.
Clinical Presentation: The patient presented with recurrent abdominal pain and fever.
Related Family and Patient History: The patient's ethnicity is not known. The patient had been suffering from abdominal pain and fever once to twice a month since the age of 26 but the clinical diagnosis was just made one year previously. She was using 2 mg/day colchicine and had no complaints.
Physical Examination: Physical examination was normal.
Laboratory Results: Blood count, electrolyte, liver function tests, sedimentation rate, C-reactive protein, fibrinogen and urinalysis were normal but serum urea (57 mmol/L) and creatinine (1.3 mg/dL) were slightly high. Proteinuria was not present in 24-hour urinalysis but microalbuminuria was found (32 mg/day). No gastrointestinal and renal biopsies were performed.

Reference: Erten, Ş., Erzurum, C., & Altunoglu, A. (2012). Three Family Members with Familial Mediterranean Fever Carrying the M694V Mutation Showed Different Clinical Presentations. *Internal Medicine*, *51*(13), 1765–1768. https://doi.org/10.2169/internalmedicine.51.7537

Clinical Vignette 18
Age: 4 month-old. **Sex:** Male. **Clinical Presentation:** The patient presented with skin rashes or systemic inflammation. At the age of 7, the patient had recurrent severe osteomyelitis episodes from 4 months of life. The patient was initially treated with prednisolone to resolve the pustular rash and significant reduction on inflammatory markers. **Related Family and Patient History:** The patient was Brazilian. Consanguinity is unknown. **Physical Examination:** After initial treatment, persistent pain on the left hip and radiological osteomyelitis were observed. **Laboratory Results:** Hemoglobin (12.5 g/dL), Leukocyte (21,710 cell/mm^3), Neutrophil (17,151 cell/mm^3), Platelet (631,000 cell/mm^3), C-Reactive Protein (384 mg/L), Erythrocyte sedimentation rate (55 mmHg)
Reference Paper: Mendonça, L. O., Grossi, A., Caroli, F., De Oliveira, R. A., Kalil, J., Castro, F. F. M., Pontillo, A., Ceccherini, I., De Barros, M. M. S. B., & Gattorno, M. (2020). A case report of a novel compound heterozygous mutation in a Brazilian patient with deficiency of Interleukin-1 receptor antagonist (DIRA). *Pediatric Rheumatology*, *18*(1). https://doi.org/10.1186/s12969-020-00454-5

Clinical Vignette 9
Age: 2 day-old. **Sex:** Male. **Clinical Presentation:** The patient presented with mouth ulcers, mild pustulosis, nail changes, and respiratory distress. The patient was previously treated with antibiotics, ibuprofen, prednisolone. **Related Family and Patient History:** The patient is from Lebanon but currently living in Sweden. Parents were non-consanguineous. The patient's birthweight was 2815 g. **Physical Examination:** Radiography showed skeletal abnormalities. The patient had widening of ribs, periosteal cloaking, periosteal elevation, multifocal osteolytic lesions, cervical vertebral fusion, and Conjunctival injection. **Laboratory Results:** Bone tissue culture was negative.
Reference Paper: Aksentijevich, I., Masters, S. L., Ferguson, P. J., Dancey, P., Frenkel, J., Van Royen-Kerkhoff, A., Laxer, R. M., Tedgård, U., Cowen, E. W., Pham, T., Booty, M. G., Estes, J. D., Sandler, N. G., Plass, N., Stone, D. L., Turner, M. L., Hill, S., Butman, J. A., Schneider, R., ... Goldbach-Mansky, R. (2009). An Autoinflammatory Disease with Deficiency of the Interleukin-1–Receptor Antagonist. *The New England Journal of Medicine*, *360*(23), 2426–2437. https://doi.org/10.1056/nejmoa0807865

Clinical Vignette 22

Age: 19 year-old.
Sex: Female.
Clinical Presentation: The patient presented with fever, dysuria, and nausea. She was initially discharged with a short course of oral amoxicillin with clavulanic acid, but no diagnosis occurred. After one month, the patient came in again with lower abdominal pain, worse epigastrium, and radiating into the right lower abdomen, with dysuria and dark orange colored urine. She was treated with simple analgesics which dropped CRP levels and was discharged. Three weeks later, she presented again with recurrent abdominal pain, accompanied with right sided pleuritic chest pain, and associated with a fever of 38.4°C.
Related Family and Patient History: The patient's ethnicity is British, but her parents were born in Turkey. She had a three year history of intermittent symptoms occurring 2-5 days, occasionally with her menstrual periods. She denied arthralgia, ulcers or skin changes.
Physical Examination: Examination showed generalized guarding in the epigastrium and suprapubic region. CT Scan showed non-specific mild fat stranding in the right distal paracolic gutter with no obvious cause. Abdominal ultrasound was unremarkable. During her second examination, urine dipstick examination was positive for blood and protein. She underwent MRI small bowel study, showing degenerative changes in L4-L5 intervertebral discs.
Laboratory Results: Arriving in, the patient was tachycardic, blood pressure (117/89 mmHg), with a low fever (37.7°C). Laboratory evaluation showed elevated white blood cell count, elevated platelets, low mean cell volume, elevated neutrophil count, elevated C-Reactive Protein count, elevated albumin, elevated total protein. Everything else was normal. C-Reactive Protein (126) during time of discharge. During her second arrival, she showed sinus tachycardia. Blood tests revealed an elevated C-Reactive Protein (109 mg/l). After her second treatment, C-Reactive Protein was 32 mg/l, but she returned again for a third visit.

Reference: Cliff-Patel, N., Yusuf, B., Hamdani, S., & Ziauddin, V. (2022). Familial Mediterranean fever: a differential diagnosis for the surgical abdomen. *JRSM Open*, *13*(9), 205427042211234. https://doi.org/10.1177/20542704221123433

Clinical Vignette 4
Age: Birth. **Sex:** Male. **Clinical Presentation:** The patient presented with respiratory distress and mild pustulosis. **Related Family and Patient History:** Patient was from the Netherlands but residing in Canada. Parents were non-consanguineous. The patient's birthweight was 2880 g. **Physical Examination:** Radiography showed skeletal abnormalities. The patient had nail changes, widening of ribs, periosteal cloaking, multifocal osteolytic lesions, and periosteal elevation, and hepatosplenomegaly. **Laboratory Results:** Bone tissue culture was negative.
Reference Paper: Aksentijevich, I., Masters, S. L., Ferguson, P. J., Dancey, P., Frenkel, J., Van Royen-Kerkhoff, A., Laxer, R. M., Tedgård, U., Cowen, E. W., Pham, T., Booty, M. G., Estes, J. D., Sandler, N. G., Plass, N., Stone, D. L., Turner, M. L., Hill, S., Butman, J. A., Schneider, R., ... Goldbach-Mansky, R. (2009). An Autoinflammatory Disease with Deficiency of the Interleukin-1–Receptor Antagonist. *The New England Journal of Medicine*, *360*(23), 2426–2437. https://doi.org/10.1056/nejmoa0807865

Clinical Vignette 36

Age: 7 year-old.
Sex: Female.
Clinical Presentation: The patient presented with fever, gross hematuria, abdominal pain, and myalgia for 4 days before she was admitted. The patient took ceftriaxone for 3 days on suspicion of a urinary tract infection. There were no recurrent attacks of fever, abdominal pain, arthralgia, or chest pain.
Related Family and Patient History: The patient's ethnicity is Turkish. The patient had a history of throat infection in the past 2 weeks. The patient's parents were non-consanguineous.
Physical Examination: Examination showed bilateral lower extremity pitting edema, generalized muscle tenderness, and abdominal tenderness. There were no rashes present.
Laboratory Results: Blood pressure (140/90 mmHg), temperature (38.7°C), hemoglobin (10 g/dl), white blood cell (11,700/mm3), platelets (352,000/mm3), C‐reactive protein (185 mg/L), erythrocyte sedimentation rate (68 mm/hour), creatinine (0.4 mg/dl), and albumin (2.4 g/dl). Liver function tests and coagulation blood tests including prothrombin time (PT), activated partial thromboplastin time (aPTT), and international normalized ratio (INR) were normal. Urinalysis revealed 2210 red blood cells per high power field which were dysmorphic.

Reference: Atikel, Y. Ö., Derinkuyu, B. E., & Bakkaloglu, S. A. (2022). Unusual presentation of familial Mediterranean fever with co‐existing polyarteritis nodosa and acute post‐streptococcal glomerulonephritis. *Clinical Case Reports*, *10*(7). https://doi.org/10.1002/ccr3.6022

Clinical Vignette 17

Age: 1 month-old.
Sex: Male.
Clinical Presentation: The patient presented with swelling and erythema about the left second distal interphalangeal joint. He was then treated with antibiotics. At 7 weeks, presented with a 24-h history of facial pustulosis, vomiting, abdominal pain, and fever and leukocytosis with neutrophilia.
Related Family and Patient History: None. Consanguinity is unknown.
Physical Examination: Radiographs of the left knee showed focal cortical destruction and periostitis suggesting congenital syphilis with periostitis of the proximal left femoral metaphysis. Chest radiograph displayed periostitis of multiple bilateral anterior ribs as well as the medial left clavicle.
Laboratory Results: None.

Reference Paper: Thacker, P. G., Binkovitz, L. A., & Thomas, K. B. (2011). Deficiency of interleukin-1-receptor antagonist syndrome: a rare auto-inflammatory condition that mimics multiple classic radiographic findings. *Pediatric Radiology*, *42*(4), 495–498. https://doi.org/10.1007/s00247-011-2208-y

Clinical Vignette 20

Age: 2 month-old.
Sex: Male.
Clinical Presentation: The patient presented with a severe pustular eruption. The patient was started on high-potency topical corticosteroid therapy, but did not respond to it. The patient developed onychomadesis and failed to thrive. The patient had pain during movement and developed desquamating scaly skin.
Related Family and Patient History: The patient had non-consanguineous parents and was Puerto Rican.
Physical Examination: Chest radiography showed patchy right upper lobe opacity, widening of the lower ribs, and abnormally close-together vertebral attachments of ribs, suggestive of decreased spine height. Osseous skeletal survey showed decreasing height of the lower thoracic vertebrae with secondary rib crowding and angulated kyphosis centered at T9–T10, an irregular and widened proximal radius; and an irregular, bulbous appearance of the left proximal femur.
Laboratory Results: Erythrocyte sedimentation rate (56 mm/h), C-reactive protein level (192.5 mg/L). Total IgE level, eosinophil count, myeloperoxidase level, biotinidase level, lymphocyte subset levels, and immunoglobulin levels were normal. The patient was also tachycardic, anemic, hematocrit of 24.9%, and was transfused with 10 mL/kg of body weight of packed red blood cells. Skin biopsy suggested infantile pustular psoriasis. Histology, however, showed inconsistency with psoriasis, and the possibility of IgA pemphigus was raised.

Reference Paper: Minkis, K., Aksentijevich, I., Goldbach-Mansky, R., Magro, C. M., Scott, R. A., Davis, J. G., Sardana, N., & Herzog, R. (2012). Interleukin 1 receptor antagonist deficiency presenting as infantile pustulosis mimicking infantile pustular psoriasis. *Archives of Dermatology*, *148*(6). https://doi.org/10.1001/archdermatol.2011.3208

Clinical Vignette 34

Age: 42 year-old.
Sex: Male.
Clinical Presentation: The patient presented with recurrent episodes of a fever and neck pain.
Related Family and Patient History: The patient's ethnicity is not known. The patient reported experiencing the same episodes during his childhood and had no related family history or consanguineous marriage. At 20, 28, 32, and 37 years of age, he visited a local hospital due to a fever, headache, neck pain, and back pain, at which time he was diagnosed with aseptic meningitis by lumbar puncture. Five years later, he again developed a fever and neck pain, and a lumbar puncture was performed. The cell count increased from the cerebrospinal fluid, and was diagnosed again with aseptic meningitis. Many of his symptoms naturally subsided within a few days, although his joint pain, fever, and headache reappeared several days later.
Physical Examination: Examination revealed tenderness in both elbows and the bilateral knee joints without apparent swelling. A neurological examination revealed no abnormalities, except for nuchal rigidity. Marked tenderness was observed in the left inner thigh and bilateral gastrocnemius muscles. An ophthalmologic examination revealed no abnormalities, such as uveitis. Radiological examinations, including brain magnetic resonance imaging (MRI), revealed no lesions. Upper and lower gastrointestinal endoscopies revealed no abnormalities, and duodenal and rectal biopsies showed no evidence of amyloidosis. However, one week after admission all of his symptoms disappeared.
Laboratory Results: During admission to the hospital, vital signs were normal. White blood cell (4,100 /μL), C-reactive protein (1.50 mg/dL), erythrocyte sedimentation rate (18 mm/h), serum Amyloid A protein (991 μg/mL). Tests showed no signs of liver/renal dysfunction or glucose intolerance. Autoantibody results: anti-dsDNA IgG: 1.5 IU/mL; antinuclear antibody: 1:40; rheumatoid factor: 2 U/mL; anti-SS-A/B antibody: negative; anti-ribonucleoprotein antibodies: 9.8 U/mL; anti-cyclic citrullinated peptide antibody: 0.6 U/mL; proteinase-3-antineutrophil cytoplasmic antibody (PR3-ANCA): <1.0; and myeloperoxidase-antineutrophil cytoplasmic antibody (MPO-ANCA): <1.0. A CSF examination revealed a cell count of 36 cells/μL with all lymphocytes and a protein concentration of 49 mg/dL. Varicella-zoster virus/herpes simplex virus (VZV/HSV) polymerase chain reaction results were negative.

Reference: Hosoi, T., Ishii, K., Tozaka, N., Kishida, D., Sekijima, Y., & Tamaoka, A. (2020). Familial Mediterranean fever is important in the differential diagnosis of recurrent aseptic meningitis in Japan. *Internal Medicine*, *59*(1), 125–128. https://doi.org/10.2169/internalmedicine.3432-19

Clinical Vignette 10
Age: 8 day-old. **Sex:** Male. **Clinical Presentation:** The patient presented with swelling of right foot and ankle, pyoderma gangrenosum, chorioamnionitis, and mild pustulosis. The patient was previously treated with interferon-γ, prednisone, and antibiotics. **Related Family and Patient History:** The patient was from Puerto Rico but was residing in the United States. Parents were non-consanguineous. The patient's birthweight was 1930 g. **Physical Examination:** Radiography showed skeletal abnormalities. Patient had widening of ribs, periosteal elevation, multifocal osteolytic lesions, and cervical vertebral fusion. **Laboratory Results:** None.
Reference Paper: Aksentijevich, I., Masters, S. L., Ferguson, P. J., Dancey, P., Frenkel, J., Van Royen-Kerkhoff, A., Laxer, R. M., Tedgård, U., Cowen, E. W., Pham, T., Booty, M. G., Estes, J. D., Sandler, N. G., Plass, N., Stone, D. L., Turner, M. L., Hill, S., Butman, J. A., Schneider, R., ... Goldbach-Mansky, R. (2009). An Autoinflammatory Disease with Deficiency of the Interleukin-1–Receptor Antagonist. *The New England Journal of Medicine*, *360*(23), 2426–2437. https://doi.org/10.1056/nejmoa0807865

Clinical Vignette 13
Age: 4 month-old. **Sex:** Female. **Clinical Presentation:** The patient presented with a high fever, and irritable swelling on the left side of the chest. **Related Family and Patient History:** The patient's ethnicity was Arab-Moslam-Persian. The patient's parents were consanguineous, and had another daughter with chronic recurrent multifocal osteomyelitis who died at age 4. **Physical Examination:** The patient had an infection in the upper respiratory tract, swelling on the left side but everything else was normal. Radiography showed bone lesions of the left sixth rib and a lytic bone lesion on the left sixth rib. **Laboratory Results:** Erythrocyte sedimentation rate (40 mm/h), anemic, leukocytosis, and thrombocytosis.
Reference Paper: Sakran, W., Shalev, S. A., El-Shanti, H., & Uziel, Y. (2013). Chronic recurrent multifocal osteomyelitis and deficiency of interleukin-1–receptor antagonist. *Pediatric Infectious Disease Journal*, *32*(1), 94. https://doi.org/10.1097/inf.0b013e3182700cc1

Clinical Vignette 21

Age: 34 year-old.
Sex: Male.
Clinical Presentation: The patient presented with frequent episodes of abdominal pain.
Related Family and Patient History: The patient's ethnicity is Japanese. 10 years before his examination, the patient had lower abdominal pain and soft stool, lasting for a few days but resolved after treatment. Similar episodes occur every 1-2 months but the patient did not come in for care because they were tolerable.
Physical Examination: Colonoscopy revealed no abnormalities. The patient had no other related history. He drinks beer (500 mL/day), smokes, and has no allergies. His father had pharyngeal cancer. The patient was afebrile (36.1℃) and other examinations were normal. Abdomen examinations were normal. Liver and renal function, along with glucose and electrolytes were normal. CT scan was normal aside from thickened abdominal membrane and edematous jejunum. Gastrointestinal fibroscopy and capsule endoscopy were performed, and revealed normal findings. Abdominal radiography showed no abnormalities aside from a thickened abdominal membrane and jejunal membrane furthered than previous.
Laboratory Results: Two years before his examination his C-reactive protein (19.22 mg/dL) and white blood cell count (6,780/μL). Upon examination, white cell count (8,000/μL), neutrophils (62.1%), hemoglobin (14.7 g/dL), C-Reactive Protein (0.49 mg/dL), platelet (258,000/μL), erythrocyte sedimentation rate (11 mm/h), and uremic acid (8.9 mg/dL). After one month, white cell count (10,900/μL), neutrophils (67.0%), C-reactive protein (12.37 mg/dL), and serum amyloid A protein (1,090 μg/mL)

Reference: Hotta, Y., Kawasaki, T., Kotani, T., Okada, H., Ikeda, K., Yamane, S., Yamada, N., Sekoguchi, S., Isozaki, Y., Nagao, Y., Murotani, M., & Oyamada, H. (2020). Familial Mediterranean Fever without Fever. *Internal Medicine*, *59*(10), 1267–1270. https://doi.org/10.2169/internalmedicine.3175-19

Clinical Vignette 2
Age: 2 week-old. **Sex:** Male. **Clinical Presentation:** The patient presented with vesicular stomatitis, mild-to-severe pustulosis, pathergy, and finger swelling. The patient received antibiotics, prednisolone, indomethacin, and IV immune globulin. Other manifestations include central nervous system vasculitis or vasculopathy, and vasculitis. **Related Family and Patient History:** Patient was from Newfoundland, Canada. Parents were non-consanguineous. The patient's birthweight was 4640 g. **Physical Examination:** Radiography showed skeletal abnormalities. The patient had nail pitting, widening of ribs, periosteal cloaking, multifocal osteolytic lesions, and periosteal elevation. **Laboratory Results:** Bone tissue culture was negative.
Reference Paper: Aksentijevich, I., Masters, S. L., Ferguson, P. J., Dancey, P., Frenkel, J., Van Royen-Kerkhoff, A., Laxer, R. M., Tedgård, U., Cowen, E. W., Pham, T., Booty, M. G., Estes, J. D., Sandler, N. G., Plass, N., Stone, D. L., Turner, M. L., Hill, S., Butman, J. A., Schneider, R., ... Goldbach-Mansky, R. (2009). An Autoinflammatory Disease with Deficiency of the Interleukin-1–Receptor Antagonist. *The New England Journal of Medicine*, *360*(23), 2426–2437. https://doi.org/10.1056/nejmoa0807865

Clinical Vignette 29

Age: 55 year-old.
Sex: Male.
Clinical Presentation: The patient presented with a seven-year history of periodic fever accompanied by chest, back or abdominal pain. During admission, antibiotics and non-steroidal analgesic agents were not effective. He was treated with three tuberculo statics for 4 weeks because of a positive tuberculin skin test, but spike fever continued. Corticosteroids were also ineffective. The fever and back pain lasted less than 24 hours. When he experienced abdominal pain accompanied by a fever, abdominal distension and Blumberg's obvious sign was noted.
Related Family and Patient History: The patient's ethnicity is not known. He had no case history of serious illness, and his family had no history of consanguineous marriage. His elder sister has diabetes mellitus and similar periodic fever. His younger brother has paroxysmal nocturnal hemoglobinuria. The patient experienced febrile attacks of over 38°C, occurring at irregular intervals 1-6 times a month, since the age of 48. He had noted that chest, back or abdominal pain simultaneously appeared with the fever since he was 49. A fever of 38-39°C with shivering developed suddenly once or twice a week. Most febrile attacks were accompanied by chest, back or abdominal pain. Untreated, the fever and pain lasted 1-2 days.
Physical Examination: The patient's physical condition was within normal limits. But on the 4th day, the patient had a fever of 38.8. There was no evidence of infectious disease or collagen disease, and malignant disease.
Laboratory Results: Obvious leukocytosis and positive CRP were recognized in the febrile phase, but there were no remarkable findings in the afebrile phase.

Reference: Takahashi, M., Ebe, T., Kohara, T., Inagaki, M., Isonuma, H., Hibiya, I., Mori, T., Watanabe, K., & Ikemoto, H. (1992). Periodic Fever Compatible with Familial Mediterranean Fever. *Internal Medicine*, *31*(7), 893–898. https://doi.org/10.2169/internalmedicine.31.893

Clinical Vignette 19

Age: 1 week-old.
Sex: Male.
Clinical Presentation: During the first week of life, the patient presented with large watery mucoid stools per day. At two months, the patient developed an extensive rash and intermittent low-grade fever. The patient also had dystrophic nails and hair, and failure to thrive 3.6 kg (<5%) at 3 months. The patient continued to have diarrhea. The patient was then transfused packed with red blood cells and albumin. He was started on intravenous antibiotics as well as topical fusidic acid ointment and moisturizers. However, he continued to have diarrhea.
Related Family and Patient History: The patient's G4P3 mother had gestational diabetes. He was the first male child of a consanguineous family of Arab ethnicity. There is a notable history of death of infants within the first 6 months after birth.
Physical Examination: The patient's birthweight was 4 kg. Evaluation after 4 months showed diffuse pustular eruption as well as extensive erythematous lesions with overlying scaly plaques overlying the patient's face, scalp, trunk and extremities. Upon handling the lower limbs, the patient was fussy.
Laboratory Results: Evaluation showed anemia (6 g/dL), hypoalbuminemia (26 g/dL) and elevated inflammatory markers (C-reactive protein 98 mg/L). Skin cultures were positive for methicillin-resistant Staphylococcus aureus. Biopsy of the skin showed pustular psoriasis. Skeletal survey revealed a focal lucent area within the proximal left tibia with adjacent periosteal reaction suggestive of osteomyelitis and widening of ribs. Laboratory results did not show infection or immunodeficiency.

Reference Paper: Abdwani, R., Abdalla, E., Masilhi, B. A., Shalaby, A., & Al-Maawali, A. (2022). Novel mutation in interleukin 1 receptor antagonist associated with chronic diarrhoea in infancy. *Journal of Paediatrics and Child Health*, *58*(1), 186–188. https://doi.org/10.1111/jpc.15440

Clinical Vignette 30

Age: 23 year-old.
Sex: Male.
Clinical Presentation: The patient presented with intermittent epigastric pain for two weeks. He took over-the-counter antacids as he ascribed this pain to acid peptic disease. The pain started again while he was sleeping. It was a tearing pain, radiating to the back with extension to the jaw, left arm, and upper abdomen.
Related Family and Patient History: The patient's ethnicity is Iranian-Persian. The patient had no history of heart disease (IHD), diabetes, hypertension, dyslipidemias, chronic kidney disease (CKD), or smoking. There was a history of periodic fever since childhood which spiked spontaneously between 37.8 to 38.9 °C and then subsided within a week after taking antipyretics. This fever was associated with myalgias, arthritis of multiple joints, and backache. There was a history of laparotomy 6 years previously, when the patient was 13 years old, with suspicion of acute abdomen. No history of no history of mouth or genital ulcers, conjunctivitis, or skin rash.
Physical Examination: There was no radio-radial or radio-femoral delay but pulsation in his right popliteal artery and dorsalis pedis artery were weak. Lungs were clear to auscultate and there were no added sounds in auscultation of the heart. No neurological finding was elicited on examination. There were no marfanoid features. ECG showed sinus tachycardia. The echocardiogram had no regional wall motion abnormality and no valvular pathology was recognized. However, there was a suspicion of an aortic dissection flap. His-troponin and creatine kinase-MB levels were normal. Computed tomography of the aorta was planned which showed a Stanford type A dissection going through the length of the thoracic and abdominal aorta into the right common iliac branch of the aorta. He was started on labetalol infusion at 2 mg/min to control his heart rate and blood pressure. The heart team immediately corrected the defect in the operating room. Surgeons undertook ascending aortic replacement with aortic arch and abdominal aortic replacement. Comprehensive post-operative treatment measures, including antipyretics, anti-infection, and nutritional support were given.
Laboratory Results: Blood pressure (176/110 mmHg), heart rate (94 beats/min), oxygen saturation (94%). After surgery, erythrocyte sedimentation rate (102 mm/hour), C-reactive protein (14.54 mg/L). blood picture, liver, kidney, and thyroid function tests were all within normal limits. Serum electrolytes, amylase, uric acid, and proteins were normal. Serologic tests were negative for tuberculosis, human immunodeficiency virus, hepatitis C virus, hepatitis B virus, syphilis, and cytomegalovirus.

Reference: Malik, A., Malik, J., Javaid, M., Khan, H. S., Mohsin, M., & Shoaib, M. (2021). A case of aortic dissection in familial Mediterranean fever. *Journal of Cardiology Cases*, *24*(6), 296–299. https://doi.org/10.1016/j.jccase.2021.05.005

Clinical Vignette 12
Age: 3 year-old. **Sex:** Male. **Clinical Presentation:** The patient presented with recurrent serositis and pancreatitis. The patient had severe pain in the back and limped. MRI showed CRMO-like lesions including multifocal bone marrow oedema on the right iliac bone and sacroiliitis. **Related Family and Patient History:** The patient had previously been hospitalized for disease flares. He had a history of fevers. The patient's parents were non-consanguineous **Physical Examination:** None. **Laboratory Results:** Inflammatory markers were elevated. Organ function was normal.
Reference Paper: Kuemmerle-Deschner, J., Welzel, T., Hoertnagel, K., Tsiflikas, I., Hospach, A., Liu, X., Schlipf, S., Hansmann, S., Samba, S. D., Griesinger, A., Benseler, S. M., & Weber, A. N. (2020). New variant in the IL1RN-gene (DIRA) associated with late-onset, CRMO-like presentation. *Rheumatology*, *59*(11), 3259–3263. https://doi.org/10.1093/rheumatology/keaa119

Clinical Vignette 39

Age: 41 year-old.
Sex: Male.
Clinical Presentation: The patient presented with intermittent chest and low back pain for the past 15 years. There was no complaint of abdominal pain or fever. He had dyspnea and atypical chest pain 3-4 times a year and had been evaluated by chest diseases and cardiology departments previously and has been found to be normal.
Related Family and Patient History: The patient's ethnicity is not known. He had a smoking history for 10 years until one year-previously. There was FMF history in his two children who were five and three years old, in his brother, sister and cousin.
Physical Examination: Physical examination was normal. Sacroiliac compression tests, fabere and fadir tests were all normal. Sacroiliac joint radiography and magnetic resonance imaging (MRI) demonstrated bilateral chronic sacroiliitis.
Laboratory Results: Leukocytes (5,100/mm3), fibrinogen (479 mg/dL), erythrocyte sedimentation rate (31 mm/h), C-reactive protein (22.8 mg/L). Renal function tests, electrolytes, liver function tests and 24-hour urine analysis were within normal limits. The rheumatoid factor (RF), antinuclear antibody (ANA), anti-ds-DNA levels and agglutination test for Brucellosis were all negative. The family history of spondyloarthropathy was negative. Human leukocyte antigen (HLA) B27 for spondyloarthropathy was negative.

Reference: Erten, Ş., Erzurum, C., & Altunoglu, A. (2012). Three Family Members with Familial Mediterranean Fever Carrying the M694V Mutation Showed Different Clinical Presentations. *Internal Medicine*, *51*(13), 1765–1768. https://doi.org/10.2169/internalmedicine.51.7537

Clinical Vignette 31

Age: 35 year-old.
Sex: Male
Clinical Presentation: The patient presented with subacute onset of chest pains and fever.
Related Family and Patient History: The patient's ethnicity is Japanese. He had previously been diagnosed with isolated adrenocorticotropic hormone deficiency and had been treated with 15 mg/d of hydrocortisone since he was 24-years-old, although his medication was intermittently taken for several months before admission. He was a non-smoker, non-alcohol consumer, and did not use illegal drugs.
Physical Examination: Ultrasonography and computed tomography scans revealed pericardial effusion with thickened pleura and pericardium. There was no evidence of viral infection or auto-inflammatory disease, and he was diagnosed with idiopathic pericarditis. Adrenal insufficiency was noted upon laboratory analysis, and he was thus treated with 100 mg/d of hydrocortisone infusion. His pericarditis recurred twice within 1 year after discharge.
Laboratory Results: White blood cell count and C-reactive protein levels were elevated.

Reference: Ashida, K., Terada, E., Nagayama, A., Sakamoto, S., Hasuzawa, N., & Nomura, M. (2020). Necessity of utilizing physiological glucocorticoids for managing familial Mediterranean fever. *American Journal of Case Reports*. https://doi.org/10.12659/ajcr.920983

Clinical Vignette 6
Age: 2 day-old **Sex:** Female **Clinical Presentation:** The patient presented with multifocal osteomyelitis, pathergy, and a fever. She was previously treated with antibiotics, indomethacin, and prednisolone. **Related Family and Patient History:** Patient was from the Netherlands. Parents were non-consanguineous. The patient's birthweight was 3000 g. **Physical Examination:** The patient had widening of ribs, periosteal cloaking, periosteal elevation, multifocal osteolytic lesions, and hepatosplenomegaly. **Laboratory Results:** Findings of bone tissue culture were negative.
Reference Paper: Aksentijevich, I., Masters, S. L., Ferguson, P. J., Dancey, P., Frenkel, J., Van Royen-Kerkhoff, A., Laxer, R. M., Tedgård, U., Cowen, E. W., Pham, T., Booty, M. G., Estes, J. D., Sandler, N. G., Plass, N., Stone, D. L., Turner, M. L., Hill, S., Butman, J. A., Schneider, R., ... Goldbach-Mansky, R. (2009). An Autoinflammatory Disease with Deficiency of the Interleukin-1–Receptor Antagonist. *The New England Journal of Medicine*, *360*(23), 2426–2437. https://doi.org/10.1056/nejmoa0807865

Clinical Vignette 28

Age: 30 year-old.
Sex: Male.
Clinical Presentation: The patient presented with a few years history of recurrent episodes of fever, abdominal pain and diarrhea that lasted for a few days and occurred a few times a year. At the time of an attack, he experienced abdominal pain spreading from the periumbilical area to the entire abdomen, a few episodes of watery diarrhea per day, and fever of approximately 38°C, all of which were alleviated within a few days by fasting and resting.
Related Family and Patient History: The patient's ethnicity is Japanese. Each time the patient visited a medical facility, he was diagnosed with acute enteritis. Between attacks, the patient was asymptomatic and had normal stools. When he noticed that the attacks had occurred once a month for 3 months in a row before visiting.
Physical Examination: Upper and lower gastrointestinal endoscopy was previously conducted with no significant abnormal findings. A biopsy specimen obtained from the edematous mucosa of the jejunum revealed partial and slight inflammatory cell infiltration and edematous changes. As a subsequently performed transanal DBE revealed no abnormal findings.
Laboratory Results: White blood cell (8,060/μL), neutrophil (72.1%), C-reactive protein (14.64 mg/dL), erythrocyte sedimentation rate (39 mm/hr). One week later, white blood cell (5,370/μL), C-reactive protein (4.69 mg/dL), erythrocyte sedimentation rate (29 mm/hr).

Reference: Matsumoto, S., Urayoshi, S., & Yoshida, Y. (2014). Familial Mediterranean fever in which Crohn's disease was suspected: a case report. *BMC Research Notes*, *7*(1). https://doi.org/10.1186/1756-0500-7-678

Clinical Vignette 1

Age: 5 month-old.
Sex: Female.
Clinical Presentation: At 3 weeks of age, the patient had right hand swelling and pain on the left hip followed by shoulder and bilateral elbow swelling. Bone scintigraphy showed multifocal osteomyelitis involvement in the ribs, clavicle and long bones. Bone biopsy showed a non-specific inflammatory reaction. Mild pustular skin rashes formed at 8 weeks on the back of the neck and upper forehead. At 5 weeks, the patient was given a broad spectrum of antibiotics for a 5 week hospitalization but there were no changes in manifestation. The patient was then clinically improved from oral prednisolone at 10 weeks
Related Family and Patient History: Ethnicity was Indian. Parents were non-consanguineous.
Physical Examination: Patient had papular skin rashes along with crusted pustules on the forehead extending to the hairline and scalp, and the posterior neck. The left hip had decreased range of motion with pain, and the left clavicle was tender and prominent. There were mixed lytic/sclerotic bone lesions in the proximal portion of the right humerus, and the left proximal femur with an adjacent periosteal reaction. There was a mild periosteal reaction on the right femur, and a proximal tibial lesion.
Laboratory Results: Hemoglobin (8.3 g/dL), Platelet (729), White blood cell (24.2 K/uL), Neutrophil absolute (12.41 K/uL), Lymphocyte absolute (9.9 K/uL), Monocyte absolute (1.89 K/uL), C-Reactive Protein (1.89 mg/L), and Erythrocyte sedimentation rate (113 mm/h).

Reference Paper: Mendonça, L. O., Malle, L., Donovan, F. X., Chandrasekharappa, S. C., Sanchez, G. a. M., Garg, M., Tedgård, U., Castells, M., Saini, S. S., Dutta, S., Goldbach-Mansky, R., Suri, D., & De Jesus, A. A. (2017). Deficiency of interleukin-1 receptor Antagonist (DIRA): report of the first Indian patient and a novel deletion affecting IL1RN. *Journal of Clinical Immunology*, *37*(5), 445–451. https://doi.org/10.1007/s10875-017-0399-1

Clinical Vignette 33

Age: 13 year-old.
Sex: Male.
Clinical Presentation: The patient presented with chest pain and dyspnea. As his signs and symptoms were strongly suggestive for cardiac tamponade, pericardiocentesis was performed, and a chest tube was inserted concerning pleural effusion. Subacute fibrinous pericarditis associated with reactive mesothelial hyperplasia was observed through the histologic assessment of the pericardium. The pericardial fluid analysis and culture were not suggestive of neither malignancy nor infection. He was discharged and placed on oral clindamycin (600 mg every 6 hours) and cefixime (400 mg once a day). After a month, he was referred for the second time, complaining of fever, tachycardia, and pleuritic chest pain. Perihilar haziness and peribronchial thickening were seen in his chest X-ray. The chest ultrasound showed left-sided pleural effusion, and it confirmed the presence of fluid around the heart with a 7 mm diameter.
Related Family and Patient History: The patient's ethnicity is not known. His parents denied any remarkable past medical history but mentioned mild influenza a few days before admission. His parents were not relatives, and his family history included some cases of arthritis and autoimmune diseases among his paternal cousins.
Physical Examination: Cardiomegaly was observed in the chest X-ray. A bilateral pleural effusion, dominant in the right side, was found through chest ultrasound. The presence of fluid with a 25 mm diameter around his heart was confirmed. Massive pericardial effusion was considered based on the findings of echocardiography. The electrocardiogram showed alternans cardiac waves; however, cardiac biomarkers were negative.
Laboratory Results: Laboratory results were positive for an elevated sedimentation rate (ESR) and an elevated C-reactive protein, in addition to mild anemia. After a month, the leukocytosis (13.34∗10^3/uL), erythrocyte sedimentation rate (57 mm/hr). Blood culture, urine culture, and serologic tests were negative. He also had unilateral pleuritis or pericarditis accompanied by severe attacks requiring bed rest.

Reference: Malek, A., Zeraati, T., Sadr-Nabavi, A., Vakili, N., & Abbaszadegan, M. R. (2022). Cardiac tamponade: a rare manifestation of familial Mediterranean fever. *Case Reports in Rheumatology*, *2022*, 1–5. https://doi.org/10.1155/2022/8334375

Clinical Vignette 40

Age: 38 year-old.
Sex: Male.
Clinical Presentation: The patient presented with repeated episodes of arthritis and fever. During the presentation he was ambulatory and appeared well. During the visit, his fever was improving and joint pain lessened.
Related Family and Patient History: The patient's ethnicity is Japanese. He had no other significant medical history.
Physical Examination: His height was 168.5 cm and weight was 62.0 kg. He had multiple acne-like skin lesions on his forehead, but there were no other abnormalities on his head, neck, eye, ear, nose, and throat. There was no lymphadenopathies or skin lesions other than those described above. Auscultation of lungs and heart were normal. There was no arthritis, joint movement impairment, or tender muscles, joints, tendons, and ligaments. His abdomen was soft and there was no organomegaly on palpitation. The rest of his physical examination was unremarkable. CT Body scan showed no abnormalities.
Laboratory Results: Blood pressure (112/79 mmHg), pulse rate (88/minute), respiratory rate (15/minute), body temperature (36.8℃). Antistreptolysin O (ASO) antibody level was low. White blood cell (6,000/mm3), neutrophil (72.9%), C-reactive protein (5.20 mg/dL), erythrocyte sedimentation rate (50 mm/hour), hemoglobin (14.7 g/dL), platelet (466,000 /μL). Serology tests for hepatitis B, hepatitis C, human T-lymphotropic virus type (HTLV)-1, mumps, syphilis, brucellosis, tsutsugamushi disease were all negative.

Reference: Iwata, K., Toma, T., & Yachie, A. (2019). Atypical Familial Mediterranean Fever Presenting with Recurrent Migratory Polyarthritis. *Internal Medicine*. https://doi.org/10.2169/internalmedicine.3001-19

Clinical Vignette 25
Age: 10.6 year-old. **Sex:** Male **Clinical Presentation:** The patient was presented with recurrent fever, aphthous stomatitis, rash, arthralgia, associated with abdominal pain, vomiting, lymphadenopathy. **Related Family and Patient History:** The patient's ethnicity is not known. **Physical Examination:** The patient gained in height for his corresponding age, and was not obese. **Laboratory Results:** Serum amyloid A (33 mg/l), C-Reactive Protein (24.8 mg/dl), Erythrocyte sedimentation rate (86), AST and ALT were 1.5 x n.v..
Reference: Maggio, M. C., Castiglia, M. S., & Corsello, G. (2019). Familial Mediterranean Fever: an unusual cause of liver disease. *Italian Journal of Pediatrics*, *45*(1). https://doi.org/10.1186/s13052-019-0712-0

Clinical Vignette 26

Age: 37 year-old.
Sex: Male.
Clinical Presentation: The patient presented with abdominal pain since the age of 34.
Related Family and Patient History: The patient's ethnicity is Japanese. He was previously diagnosed with acute gastroenteritis, he was treated with an antibiotic and a medication for intestinal dysfunction, and the symptoms improved after a few days. However, the patient returned with an increasing frequency of abdominal pain and severity. With further examination, he was diagnosed with bowel obstruction. Because PCT was positive, the administration of levofloxacin (500 mg/day) was started to treat a possible bacterial infection. Abdominal symptoms resolved and CRP lowered. The next day, patency capsule endoscopy was performed because conditions such as Crohn's disease were suspected.
Physical Examination: Examination revealed prominent rebound tenderness in the left lower quadrant of the abdomen and the supraumbilical region. A plain abdominal X-ray film revealed air-fluid levels in the small bowel. Abdominal CT showed a slight dilation of the bowel and the accumulation of fluid. After treatment with levofloxacin, an abdominal X-ray film revealed air-fluid levels in the small bowel again. Bowel obstruction was suspected, and so a long tube that could reach the small bowel was inserted for decompression and small bowel imaging revealed jejunal stenosis.
Laboratory Results: White blood cell (8,400/μL), neutrophil (87.5%), C-Reactive Protein (24.78 mg/dL), procalcitonin (0.85 ng/mL).

Reference: Kasamaki, K., Kusano, C., Ikehara, H., Suzuki, S., Esaki, M., Irie, A., Hayashi, K., Okuno, H., Moriyama, M., & Gotoda, T. (2019). Familial Mediterranean Fever with Small Bowel Stenosis. *Internal Medicine*. https://doi.org/10.2169/internalmedicine.2293-18

Clinical Vignette 3
Age: Birth. **Sex:** Female. **Clinical Presentation:** The patient presented with mild pustulosis and aspiration pneumonia. At 2 weeks, the patient developed a rash. The patient previously received IV immune globulin, antibiotics, etanercept, indomethacin, prednisolone, methotrexate, cyclosporine, azathioprine, and thalidomide. **Related Family and Patient History:** Patient was from the Netherlands. Parents were non-consanguineous. The patient's birthweight was not known. **Physical Examination:** Radiography showed skeletal abnormalities. The patient had widening of ribs, periosteal cloaking, multifocal osteolytic lesions, and periosteal elevation, cervical vertebral fusion, and hepatosplenomegaly. **Laboratory Results:** Bone tissue culture was negative.
Reference Paper: Aksentijevich, I., Masters, S. L., Ferguson, P. J., Dancey, P., Frenkel, J., Van Royen-Kerkhoff, A., Laxer, R. M., Tedgård, U., Cowen, E. W., Pham, T., Booty, M. G., Estes, J. D., Sandler, N. G., Plass, N., Stone, D. L., Turner, M. L., Hill, S., Butman, J. A., Schneider, R., ... Goldbach-Mansky, R. (2009). An Autoinflammatory Disease with Deficiency of the Interleukin-1–Receptor Antagonist. *The New England Journal of Medicine*, *360*(23), 2426–2437. https://doi.org/10.1056/nejmoa0807865

Clinical Vignette 14

Age: 37 weeks-old.
Sex: Female.
Clinical Presentation: The patient presented with an abscess on the left index finger and nail shedding.
Related Family and Patient History: The patient has consanguineous parents and was Puerto Rican. At 7 days old, the patient developed pustules on the left ankle resolved by antibiotics. They later recurred with gastroesophageal reflux and failure to thrive. The patient was previously treated with methylprednisolone and corticosteroids.
Physical Examination: Bone lesions were found on the right hip. Hip pain continued, and pustular lesions increased pathergy over minor trauma areas. Radiography showed multifocal periostitis and osteomyelitis.
Laboratory Results: Tested negative for any bacterial or fungal pathogens. Skin biopsy showed epidermal acanthosis with intracorneal and intraepidermal neutrophilic microabscesses, mild papillary dermal edema, and a superficial interstitial infiltrate of neutrophils and occasional eosinophils. Direct immunofluorescence, periodic acid Schiff and potassium hydroxide staining were negative. High C-Reactive Protein, Erythrocyte sedimentation rate, and white blood cell count.

Reference Paper: Schnellbacher, C., Ciocca, G., Menendez, R., Aksentijevich, I., Goldbach-Mansky, R., Duarte, A. M., & Rivas-Chacon, R. (2012). Deficiency of interleukin-1 receptor antagonist responsive to anakinra. *Pediatric Dermatology*, *30*(6), 758–760. https://doi.org/10.1111/j.1525-1470.2012.01725.x

Clinical Vignette 23

Age: 26 year-old.
Sex: Male
Clinical Presentation: The patient presented with abdominal pain and fever.
Related Family and Patient History: The patient's ethnicity is not known. The patient had a history of ulcerative colitis treatment, bloody stools, and abdominal pain at 19 years of age. He was previously diagnosed with ulcerative colitis. The patient was treated with 5‐aminosalicylate (5ASA) after induction of remission using prednisolone (PSL). However, his symptoms flared and was administered 30 mg/day of PSL. During his previous follow up, he complained of abdominal pain and diarrhea. 30 mg/day of PSL were administered, and did not improve with 40 mg/day of PSL.
Physical Examination: Colonoscopy showed loss or reduction of vascular permeability throughout the mucosa of the colon, with coarse mucosa, erythema, and adhesions of purulent secretions. Computed tomography revealed thickening of the colon and no abnormality in the small intestine.
Laboratory Results: White blood count (8400/μl), neutrophil (87.5% neutrophils), C‐reactive protein level (24.78 mg/dl), amyloid protein (1568.5 μg/ml).

Reference: Ariga, H., Kunisaki, R., Ojima, T., Suzuki, S., Okada, K., & Kashimura, J. (2023). Familial Mediterranean fever with colonic lesions: A case report. *DEN Open*, *4*(1). https://doi.org/10.1002/deo2.246

Clinical Vignette 7
Age: 2.5 week-old. **Sex:** Female. **Clinical Presentation:** The patient presented with oral candidiasis, pustular dermatitis on cheeks, and severe pustulosis. **Related Family and Patient History:** Patient was from the Netherlands. Parents were non-consanguineous. The patient's birthweight was 3780 g. **Physical Examination:** Radiography showed skeletal abnormalities. Patient had widening of ribs, periosteal cloaking, and hepatosplenomegaly. **Laboratory Results:** Bone tissue culture was not tested.
Reference Paper: Aksentijevich, I., Masters, S. L., Ferguson, P. J., Dancey, P., Frenkel, J., Van Royen-Kerkhoff, A., Laxer, R. M., Tedgård, U., Cowen, E. W., Pham, T., Booty, M. G., Estes, J. D., Sandler, N. G., Plass, N., Stone, D. L., Turner, M. L., Hill, S., Butman, J. A., Schneider, R., ... Goldbach-Mansky, R. (2009). An Autoinflammatory Disease with Deficiency of the Interleukin-1–Receptor Antagonist. *The New England Journal of Medicine*, *360*(23), 2426–2437. https://doi.org/10.1056/nejmoa0807865

Clinical Vignette 15

Age: 1.5 months-old.
Sex: Male.
Clinical Presentation: The patient presented with recurrent episodes of fever and mucositis. Progression occurred into erythematous, scaling skin, pustular rash, and lessened with advancing age. He also presented with nail dystrophy, chronic fatigue, paleness, developmental and growth retardation. The patient also had problems with ambulation from debilitating chronic musculoskeletal pain, epiphyseal overgrowth of knees, and peripheral joint contractures without axial joint involvement.
Related Family and Patient History: The patient was Iranian Persian. The patient's parents were consanguineous. The patient had many previous visits due to pathologic fracture of the right wrist, sterile osteomyelitis, arthritis, pneumonia, or cytomegalovirus-associated enteritis.
Physical Examination: Examination showed height and weight were below the 5th percentile.
Laboratory Results: None.

Reference Paper: Ziaee, V., Youssefian, L., Faghankhani, M., Jazayeri, A., Saeidian, A. H., Vahidnezhad, H., & Uitto, J. (2020). Homozygous IL1RN Mutation in Siblings with Deficiency of Interleukin-1 Receptor Antagonist (DIRA). *Journal of Clinical Immunology*, *40*(4), 637–642. https://doi.org/10.1007/s10875-020-00767-w

Clinical Vignette 37

Age: 21 year-old.
Sex: Male.
Clinical Presentation: The patient presented with refractory diarrhea and weight loss of 14 kg over the past two years. He had a recurrent fever, abdominal pain, anal fistula and stomatitis.
Related Family and Patient History: The patient's ethnicity is Japanese. His father and one of his brothers had ulcerative colitis.
Physical Examination: Colonoscopy revealed longitudinal ulcers in the terminal ileum and aphthous erosions in the colorectum. Esophagogastroduodenoscopy revealed multiple linear erosions in the gastric corpus and circular erosions in the duodenal second portion.
Laboratory Results: Biopsy from these lesions failed to detect epithelioid cell granulomas.

Reference: Asakura, K., Yanai, S., Nakamura, S., Kawaski, K., Eizuka, M., Ishida, K., Endo, M., Sugai, T., Migita, K., & Matsumoto, T. (2018). Familial Mediterranean fever mimicking Crohn disease. *Medicine*, *97*(1), e9547. https://doi.org/10.1097/md.0000000000009547

Clinical Vignette 27

Age: 37 year-old.
Sex: Male.
Clinical Presentation: The patient presented with recurrent attacks of generalized abdominal pain, nausea, vomiting, fever, arthralgia, and fatigue for the past 4 years. The symptoms were chronic and intermittent, and increased in frequency of the past 2 years. The pain was described as sharp, radiating to the back, and associated with multiple episodes of fasting diarrhea. Regarding his acute appendicitis and small bowel obstruction, diagnostic laparoscopy with appendectomy and a 20-cm small bowel resection was completed. Pathology showed inflamed jejunum with fibrous obliteration, serosal adhesions, and enteritis with cryptitis, but a normal appendix.
Related Family and Patient History: The patient's ethnicity is of Irish, German, and Spanish descent. Pertinent family history includes fibromyalgia and rheumatoid arthritis in his mother and ulcerative colitis in his maternal aunt. He was previously admitted for severe dehydration secondary to his conditions. During his recent hospitalization, he complained of right lower quadrant abdominal pain, fevers, and subacute worsening diarrhea.
Physical Examination: Computed tomography scan of his abdomen showed findings concerning acute appendicitis and small bowel obstruction. Inflammatory bowel disease was effectively ruled out with negative biopsies, endoscopy, video capsule endoscopy, and magnetic resonance enterography.
Laboratory Results: Antinuclear antibody test (1:160, homogenous pattern). C-reactive protein (5.7 mg/dL), erythrocyte sedimentation rate (23 mm/hr), thyroid-stimulating hormone (10 IU/mL).

Reference: Evans, N., Ray, J., & Prather, C. M. (2021). Atypical Autosomal-Dominant inheritance of familial Mediterranean fever. *ACG Case Reports Journal*, *8*(3), e00525. https://doi.org/10.14309/crj.0000000000000525

Clinical Vignette 11

Age: 37 weeks-old.
Sex: Male.
Clinical Presentation: The patient presented with pustular skin lesions and fever after his first month born. During the first week of life, erythematous and scaly eruptions over the perineum and scalp. Lesions were first on the forehead and moved throughout the body. Chemical bath with borique followed by liquid vaseline was recommended. Antibiotics and eye drops were prescribed for conjunctivitis. Following treatment, the patient had failure of growth and loss of appetite. He had a continuous fever with no improvement from antimicrobial therapies.
Related Family and Patient History: The patient had Turkish parents and they were non-consanguineous.
Physical Examination: The patient had excessive abdominal distention. His left wrist was swollen and erythematous was tender with palpation and motion. His nails were dystrophic.
Laboratory Results: Skin biopsy was performed and revealed signs of generalized pustular psoriasis. Blood and urine samples were negative. Hemoglobin (7.3 g/dl), white blood cell count (12,980 cells/mm3), neutrophils (88%), blood platelets levels (980,000 cells/mm3), erythrocyte sedimentation rate (81 mm/hour), and C-reactive protein (11.3 mg/dl).

Reference Paper: Sözeri, B., Gerçeker-Türk, B., Yıldız-Atıkan, B., Mir, S., & Berdeli, A. (2018). A novel mutation of interleukin-1 receptor antagonist (il1rn) in a dira patient from turkey: diagnosis and treatment. *Turkish Journal of Pediatrics*, *60*(5), 588. https://doi.org/10.24953/turkjped.2018.05.020

Clinical Vignette 5
Age: Birth. **Sex:** Male. **Clinical Presentation:** The patient presented with joint swelling (proximal interphalangeal joint and wrist), stomatitis, severe pustulosis, and a rash on the forehead. The patient also had Interstitial lung disease, hypotonia, and developmental delay. The patient was previously treated with prednisone, methotrexate, antibiotics, and cyclosporine. **Related Family and Patient History:** Patient was from the Netherlands. Parents were non-consanguineous. The patient's birthweight was 2880 g. **Physical Examination:** Radiography showed skeletal abnormalities. The patient had widening of ribs, periosteal cloaking, multifocal osteolytic lesions, periosteal elevation, cervical vertebral fusion, and hepatosplenomegaly. **Laboratory Results:** Bone tissue culture was negative.
Reference Paper: Aksentijevich, I., Masters, S. L., Ferguson, P. J., Dancey, P., Frenkel, J., Van Royen-Kerkhoff, A., Laxer, R. M., Tedgård, U., Cowen, E. W., Pham, T., Booty, M. G., Estes, J. D., Sandler, N. G., Plass, N., Stone, D. L., Turner, M. L., Hill, S., Butman, J. A., Schneider, R., ... Goldbach-Mansky, R. (2009). An Autoinflammatory Disease with Deficiency of the Interleukin-1–Receptor Antagonist. *The New England Journal of Medicine*, *360*(23), 2426–2437. https://doi.org/10.1056/nejmoa0807865

Clinical Vignette 32

Age: 65 year-old.
Sex: Male
Clinical Presentation: The patient presented with frequent episodes of abdominal pain and fever. His fever was 38°C, and had abdominal pain, watery diarrhea, and constipation.
Related Family and Patient History: The patient's ethnicity is not known. Seven years before admission, the patient experienced abdominal pain and high-grade fever, lasting for a few days and spontaneously resolving without treatment. Similar attacks were noted once every two months, but he did not seek medical care because the symptoms were tolerable and spontaneously relieved within a few days.
Physical Examination: None.
Laboratory Results: white blood cell (11640/μL), C-reactive protein (14.7 mg/dL), and erythrocyte sedimentation rate (59 mm/h).

Reference: Toshida, M., Konishi, Y., Ikenouchi, A., Okamoto, N., & Yoshimura, R. (2021). Colchicine-Resistant familial Mediterranean fever with depressive state successfully treated with Escitalopram. *Cureus*. https://doi.org/10.7759/cureus.15145