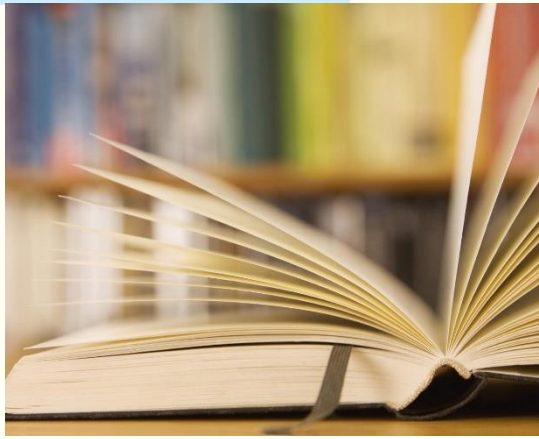
# Hypercalcemia in a CKD Patient



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**1399/8/6- 27/10/2020**

# Case

- A 66 y/o woman consulted for azotemia (Cr=2) **before coronary CT angiogram** b/c of weakness for 2 weeks.
- Before admission: **Cr =3.6 mg/dl and serum Ca =14.6** mg/dl.
- Vital sign=Nl, O2sat=97%, echo: EF=60%

# Case…

**A 66 y/o woman Cr =3.6 mg/dl and serum Ca =14.6**

**PMH: no DM, no HTN**, minor thalassemia, Hypothyroidism, vitilligo,

**Hospital admission 3 yrs ago** due to LBP, abdominal pain, mild splenomegaly; and multiple thoracic LAP was detected.

Lab: serum Cr=1.2, serum Ca= 8.9, P= 4.4, Alb=4, ESR=10, Hb=12.7, extensive work up for GI, malignancy, and discharged with Dx of abdominal herpes zoster after developing vesicular rash.

# Case..

- **A 66 y/o woman Cr =3.6 mg/dl and serum Ca =14.6**
- Lab: ESR: 35, Hb:10, U/A: pr+,
- **Protein= 434mg**
- 24 h ur Cr= 1147
- **Ca= 418,**
- **Vol=3100**
- CRP=17, Mg=2.1, HCO3=22, pH=7.38, Pco2= 38.5 coagula=nl,
- US: LK= 116 mm , RK= 112 mm, no stone or hydronephrosis, with spleen diameter=157mm,

# Case…

| Lab value | 99 | 96 | Lab value | 99 | 96 |
|---|---|---|---|---|---|
| Cr | 3.6 → 2.2 | 1.2 → 1.5 | LFT | Nl | Nl |
| **Ca** | **14.6 → 10.4** | 8.9 | Gama GT | __ | 6 (5-36) |
| Hb | 10 | 12.7 | TSH | 5.4 | Nl |
| Alb | 3.4 | 4 | ANA, ANCA | Neg | Neg |
| ESR | 35 | 10 | Anti ds DNA | Neg | Neg |
| P | 3 | 4.4 | SPEP | IgG ↑ | IgG ↑ |
| U/A | 1018-pH=6, Pro+ | __ | Tumor markers, CD | __ | Nl |
| 24 hr ur pro | 434 | __ | ACE | __ | 79 (8-65) |
| **PTH** | **19 (15-68)** | __ | Immunofixation | Polyclonal | |
| IGRA | Neg | __ | Wright, coombs | __ | Neg |
| 25 OH Vt D3 | 23(30-50) | | | | |

# Etiology of hypercalcemia

***Primary hyperparathyroidism*** **and** ***malignancy***

are the **most common cause** accounting for greater than 90 percent of cases.

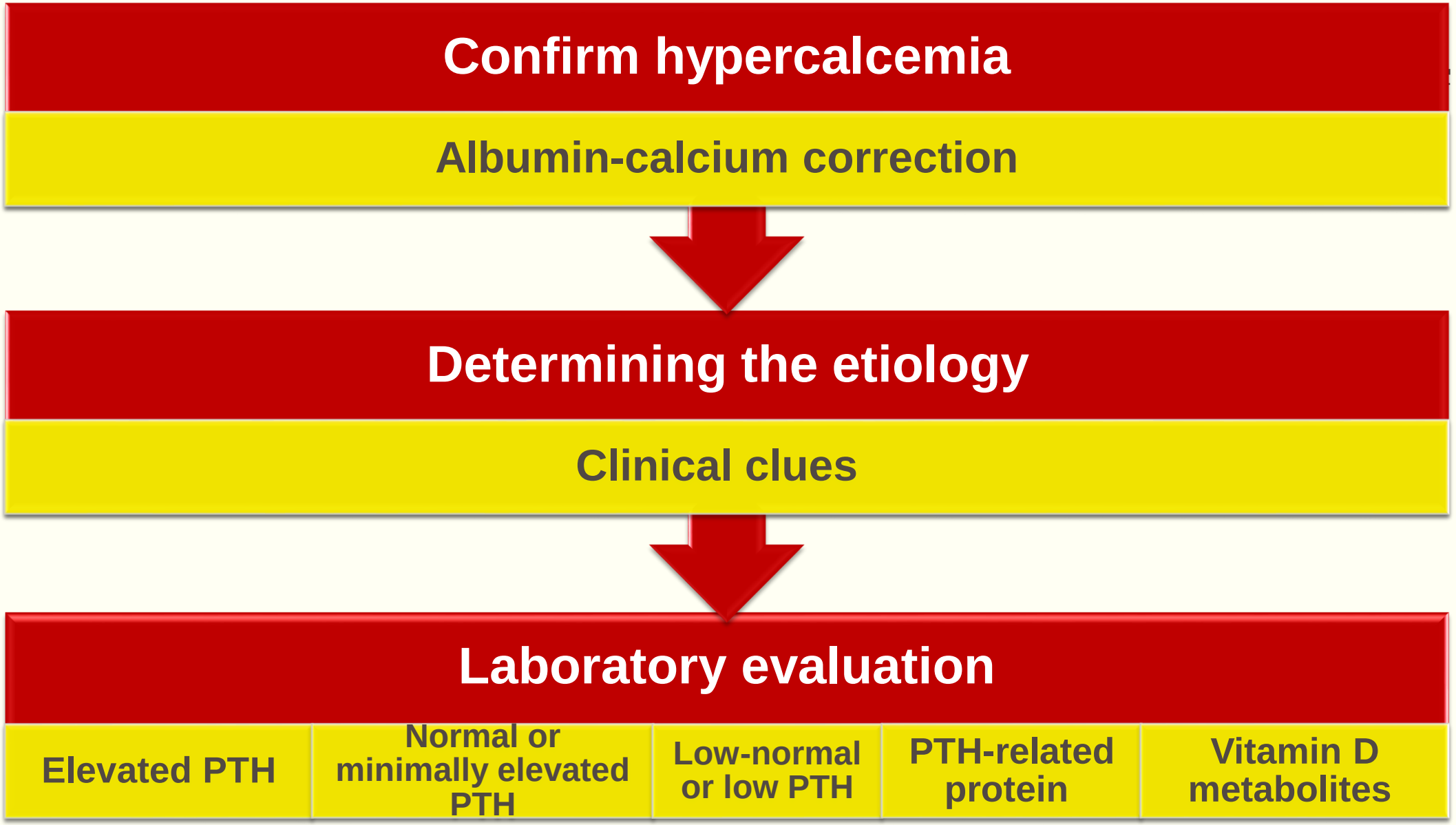
# Etiology of Hypercalcemia

| Parathyroid mediated | Non-parathyroid mediated | Medications | Miscellaneous |
|---|---|---|---|
| Primary hyperparathyroidism (sporadic) | Hypercalcemia of malignancy | Thiazide diuretics | Hyperthyroidism |
| Inherited variants | PTHrP | Lithium | Acromegaly |
| Multiple endocrine neoplasia (MEN) syndromes | Increased calcitriol (activation of extrarenal 1-alpha-hydroxylase) | Teriparatide | Pheochromocytoma |
| Familial isolated hyperparathyroidism | Osteolytic bone metastases and local cytokines | Abaloparatide | Adrenal insufficiency |
| Hyperparathyroidism-jaw tumor syndrome | Vitamin D intoxication | Excessive vitamin A | Immobilization |
| Familial hypocalciuric hypercalcemia | Chronic granulomatous disorders | Theophylline toxicity | Parenteral nutrition |
| Tertiary hyperparathyroidism (renal failure) | | | Milk-alkali syndrome |

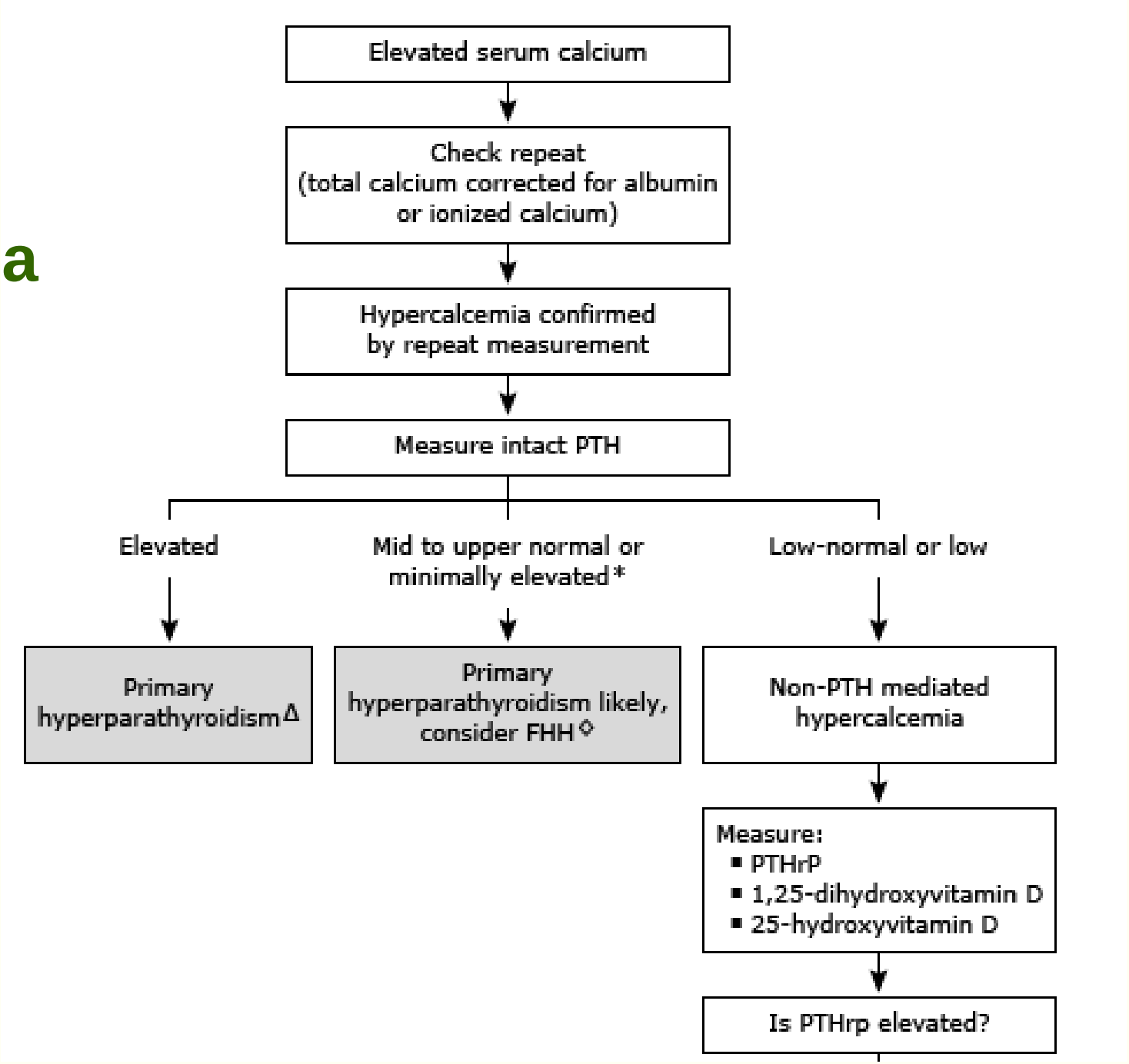
# Clinical manifestations of hypercalcemia

| Renal | Gastrointestinal | Musculoskeletal | Neurologic | Cardiovascular |
|---|---|---|---|---|
| **Polyuria** | Anorexia, nausea, vomiting | Muscle weakness | Decreased concentration | Shortening of the QT interval |
| Polydipsia | Bowel hypomotility and constipation | Bone pain | Confusion | Bradycardia |
| Nephrolithiasis | Pancreatitis | Osteopenia/osteoporosis | Fatigue | Hypertension |
| ***Nephrocalcinosis*** | Peptic ulcer disease | | Stupor, coma | |
| **Distal renal tubular acidosis** | | | | |
| Nephrogenic diabetes insipidus | | | | |
| **Acute and chronic renal insufficiency** | | | | |

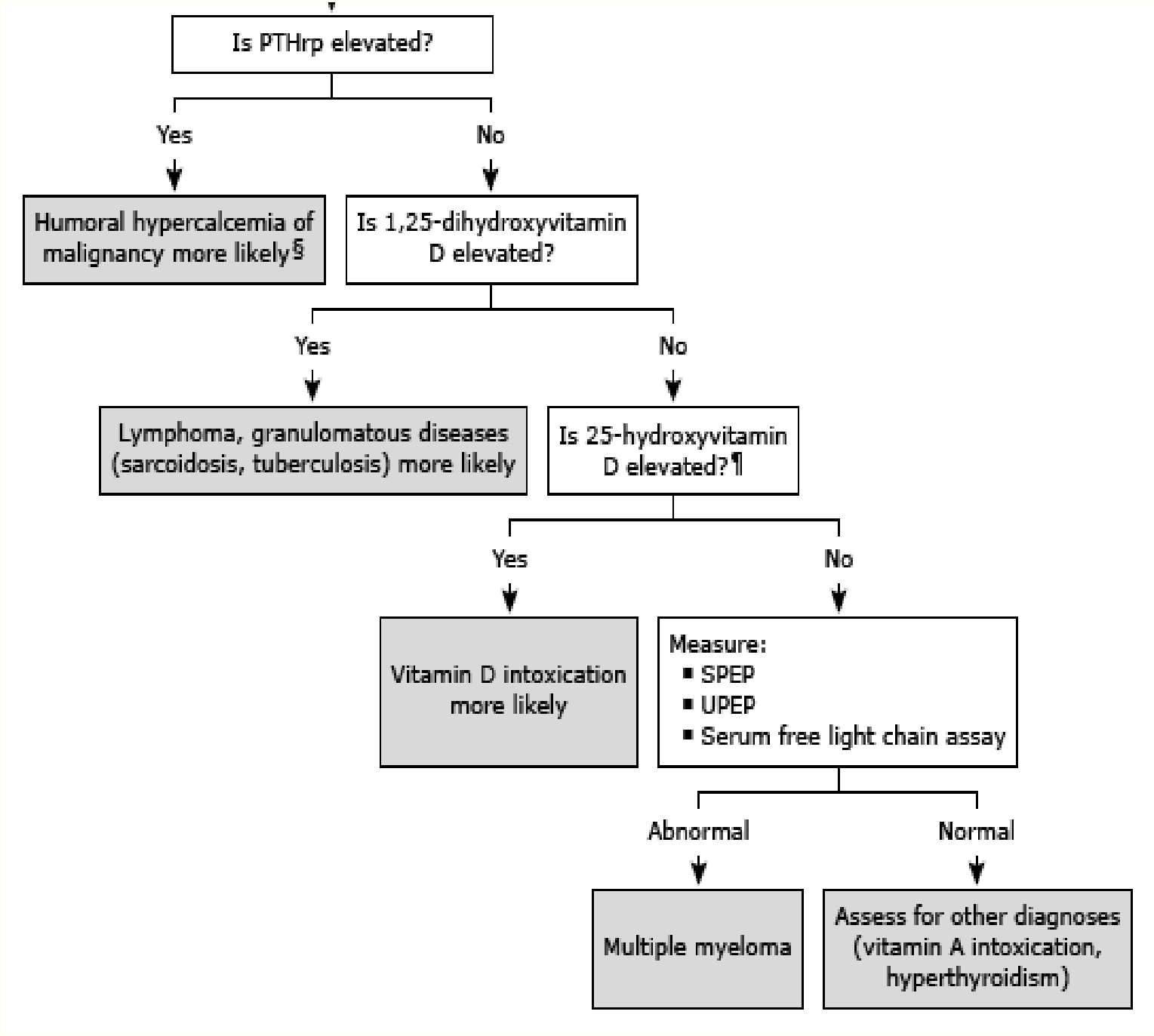
# Diagnostic approach to hypercalcemia:



# Diagnostic approach to hypercalcemia



# Diagnostic approach to hypercalcemia



# Case…

## In hospital therapy:

1. **Normal saline 4 Lit /day**
2. **Lasix  20 mg bid**
3. **Calcitonin Nasal spray 300 IU TDS**
4. **Denosumab (prolia) 120 mg**

# Treatment of hypercalcemia

## INTERPRETATION OF SERUM CALCIUM:

In **hypoalbuminemia;**

- Total serum calcium concentration may be normal when serum ionized calcium is elevated

In **hyperalbuminemia**:

- Severe volume depletion, multiple myeloma (calcium-binding paraprotein); increased protein binding of calcium, cause an elevation in the serum total calcium without rise in the serum ionized calcium.
- This phenomenon is called **pseudohypercalcemia (or factitious hypercalcemia).**

# INDICATIONS FOR TREATMENT

## Mild hypercalcemia (Corrected Calcium <12 mg/dL)

- No immediate treatment, avoid thiazide diuretics and lithium carbonate therapy, volume depletion, prolonged bed rest or inactivity, and a high calcium diet (>1000 mg/day).

## Moderate hypercalcemia (12 ≤ Calcium <14 mg/dL)

- Chronic: may not require immediate therapy
- **Acute:** requires **more aggressive therapy** (saline, bisphosphonate)

## Severe hypercalcemia (Calcium >14 mg/dL)

- Or changes in sensorium (eg, lethargy, stupor): **aggressive**

# Immediate therapy

1. **Volume expansion** with **isotonic saline** at an initial rate of 200 to 300 mL/hour, maintain urine output at 100 to 150 mL/hour.
2. **Loop diuretic** therapy to directly increase calcium excretion is not recommended except in the presence of heart failure or renal failure

# Immediate therapy

3. Salmon **Calcitonin** (4 IU/kg) SC or IM q 12 hrs and repeat measurement of serum calcium in several hours.

- Reduce serum calcium: 1- increasing **renal calcium excretion** and more importantly, 2- decreasing **bone resorption** via interference with osteoclast function.
- Safe and relatively nontoxic, mild nausea.
- Relatively weak agent, works rapidly, lowering the serum calcium maximum of 1 to 2 mg/dL beginning within four to six hours
- **Tachyphylaxis** to calcitonin **after 24 to 48 hours**, limited to this time period. **Nasal application is not efficacious.**
- Both reduce Ca within 12 to 48 hours.

# Immediate therapy..

- **Zoledronic acid** (ZA; 4 mg intravenously [IV] over 15 minutes) or
- **Pamidronate** (60 to 90 mg over two hours).
- ZA is preferable because it is superior to pamidronate in reversing hypercalcemia related to malignancy.
- **Denosumab** can be administered concurrently with calcitonin, if bisphosphonates are contraindicated (eg, due to severe renal impairment),
- Avoidance of calcium-containing foods and supplements and vitamin D.

## Treatment of hypercalcemia

# Bisphosphonates (moderate to severe hypercalcemia)

- **Adsorb** to the surface of **bone hydroxyapatite** and **inhibit calcium release** by interfering with osteoclast-mediated bone resorption.
- Effective in treating hypercalcemia resulting from excessive bone resorption of any cause (malignancy, metastatic cancer of bone).
- Relatively nontoxic compounds, more potent than calcitonin and saline.
- Maximum effect occurs in two to four days

## Treatment of hypercalcemia

# Bisphosphonates..

**Choice of drug:**

- Pamidronate,
- Zoledronic acid [ZA],
- Ibandronate,
- Clodronate, and
- Etidronate

## Treatment of hypercalcemia

# Bisphosphonates.. Choice of drug..

- **Zoledronic acid (ZA)**: (malignancy) **4 mg IV over 15 minutes**.
- **Pamidronate** (when ZA not available): 60-90 mg infusion times (two to four hours, calcium concentrations begin to decrease in one or two days.
- ZA preferred: available, more potent, short administration (15 minutes compared with two hours).
- In clinical trials of ZA for the treatment of hypercalcemia of malignancy, patients with serum creatinine concentrations as high as 4.5 mg/dL were eligible for participation.

# Zoledronic Acid Is Superior to Pamidronate in the Treatment of Hypercalcemia of Malignancy: A Pooled Analysis of Two Randomized, Controlled Clinical Trials

By P. Major, A. Lortholary, J. Hon, E. Abdi, G. Mills, H.D. Menssen, F. Yunus, R. Bell, J. Body, E. Quebe-Fehling, and J. Seaman

***Purpose:*** **Two identical, concurrent, parallel, multicenter, randomized, double-blind, double-dummy trials were conducted to compare the efficacy and safety of zoledronic acid and pamidronate for treating hypercalcemia of malignancy (HCM).**

***Patients and Methods:*** **Patients with moderate to severe HCM (corrected serum calcium [CSC] ≥ 3.00 mmol/L [12.0 mg/dL]) were treated with a single dose of zoledronic acid (4 or 8 mg) via 5-minute infusion or pamidronate (90 mg) via 2-hour infusion. A protocol-specified pooled analysis of the two parallel trials was performed. Clinical end points included rate of complete response by day 10, response duration, and time to relapse.**

***Results:*** **Two hundred eighty-seven patients were randomized and evaluated for safety; 275 were evaluated for efficacy. Both doses of zoledronic acid were superior to pamidronate in the treatment of HCM. The complete response rates by day 10 were 88.4% ($P$ = .002), 86.7% ($P$ = .015), and 69.7% for zoledronic acid 4 mg and 8 mg and pamidronate 90 mg, respectively. Normalization of CSC occurred by day 4 in approximately 50% of patients treated with zoledronic acid and in only 33.3% of the pamidronate-treated patients. The median duration of complete response favored zoledronic acid 4 and 8 mg over pamidronate 90 mg with response durations of 32, 43, and 18 days, respectively.**

***Conclusion:*** **Zoledronic acid is superior to pamidronate; 4 mg is the dose recommended for initial treatment of HCM and 8 mg for relapsed or refractory hypercalcemia.**



*Journal of Clinical Oncology*, Vol 19, No 2 (January 15), 2001: pp 558-567

## Treatment of hypercalcemia

# Bisphosphonates.. Choice of drug..

- **Ibandronate** appears to be as effective as **pamidronate.** 2-4 mg IV administered over two hours.
- **Alendronate** and **risedronate:** potent, **orally**, **neither** for the treatment of **severe or acute** hypercalcemia.

- **Repetitive IV use of bisphosphonates** has been associated with risk of developing **osteonecrosis of the jaw** in patients with **multiple myeloma or metastatic bone disease**.

## Treatment of hypercalcemia

# Bisphosphonates.. Side effects

- Flu-like symptoms (fever, arthralgias, myalgia, fatigue, bone pain),
- Ocular inflammation (uveitis),
- Hypocalcemia,
- Hypophosphatemia,
- Impaired renal function,
- Nephrotic syndrome,
- Osteonecrosis of the jaw, and atypical femur fractures (in patients who require long-term therapy)

## Treatment of hypercalcemia

# Bisphosphonates.. **Dosing in renal impairment**

- **Creatinine >4.5 mg/dL,**
- Adequate hydration with **saline** and
- Treatment with a reduced dose and/or slower infusion rate (4 mg ZA over 30 to 60 minutes, 30 to 45 mg pamidronate over four hours, 2 mg ibandronate over one hour) may minimize risk.

## Treatment of hypercalcemia

# Glucocorticoids

- Increased calcitriol production can occur in patients with chronic granulomatous diseases (eg, sarcoidosis) and in occasional patients with lymphoma.
- Glucocorticoids (eg, prednisone in a dose of 20 to 40 mg/day) reduce serum calcium within two to five days by decreasing calcitriol production by the activated mononuclear cells in the lung and lymph nodes.

## Treatment of hypercalcemia

# Denosumab

## Indication:

- Hypercalcemia that is refractory to zoledronic acid (ZA)
- **Bisphosphonates are contraindicated due to severe renal impairment.**
- Unlike bisphosphonates, **not cleared by the kidney**, **no restriction in chronic kidney disease,**
- Improved serum calcium within **two to four days**
- With one or two days of vitamin D, 50,000 international units daily for prevention of hypocalcemia before obtaining serum level of 25 OH VD

## Treatment of hypercalcemia

# Calcimimetics

**Cinacalcet** only available.

Elevated calcium-phosphorous product and secondary hyperparathyroidism.

# Immediate therapy..

- **Hemodialysis** should be considered, in addition to the above treatments, **if:**

1. Serum calcium concentrations in the range of 18 to 20 mg/dl
2. Neurologic symptoms but a stable circulation
3. Severe hypercalcemia complicated by renal failure.

## Treatment of hypercalcemia

# Dialysis

**Hemodialysis** with **little or no calcium in the dialysis fluid** and **peritoneal dialysis** (though it is **slower**) are treatments of last resort.

1. Severe malignancy-associated hypercalcemia and renal insufficiency or heart failure.
2. **Hemodialysis without renal failure**: dialysis solution with **phosphorus (4 mg**/dL) resulted in rapid **correction** of all abnormalities, mental status changes, and **hypophosphatemia due to primary hyperparathyroidism**.

# Case…

## Multislice Chest Ct without contrast and Kidney biopsy was done

**1396**

**Spiral CT**

**± contrast**

**Chest:**

**Multiple LAP in mediastinum, hilar, tracheal, carina, supra clavicular, …**

**Abdomen, pelvic:**

**Mild splenomegaly**

**Lymph node FNA: reactive**

**BMA, BMB: Nl, mild hypocellular**

**1399**

**MDCT**

**No contrast**

**Chest:**

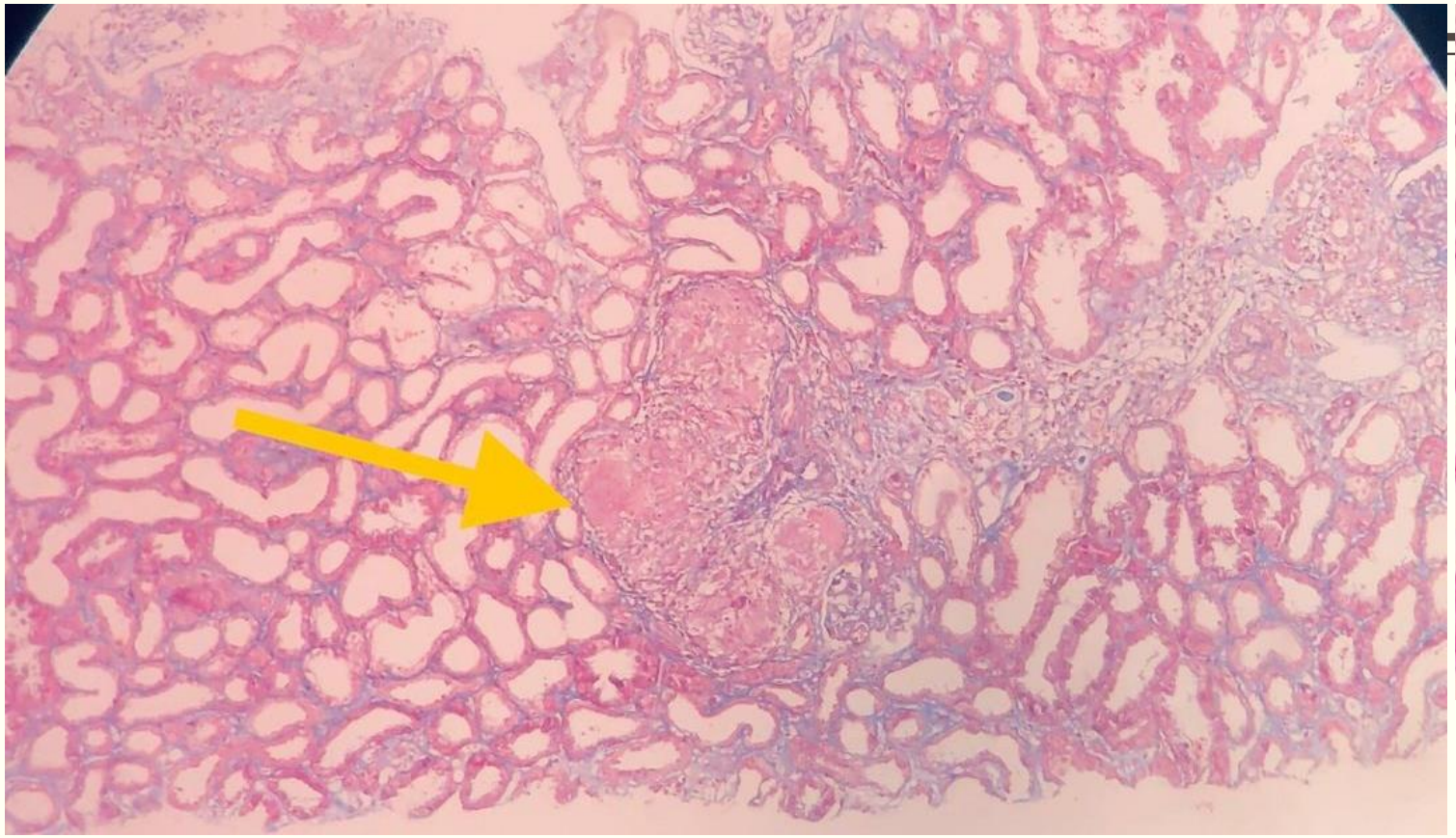
**No mediastinal LAP,**

**Hilar LAP can not diagnose due to no contrast.**

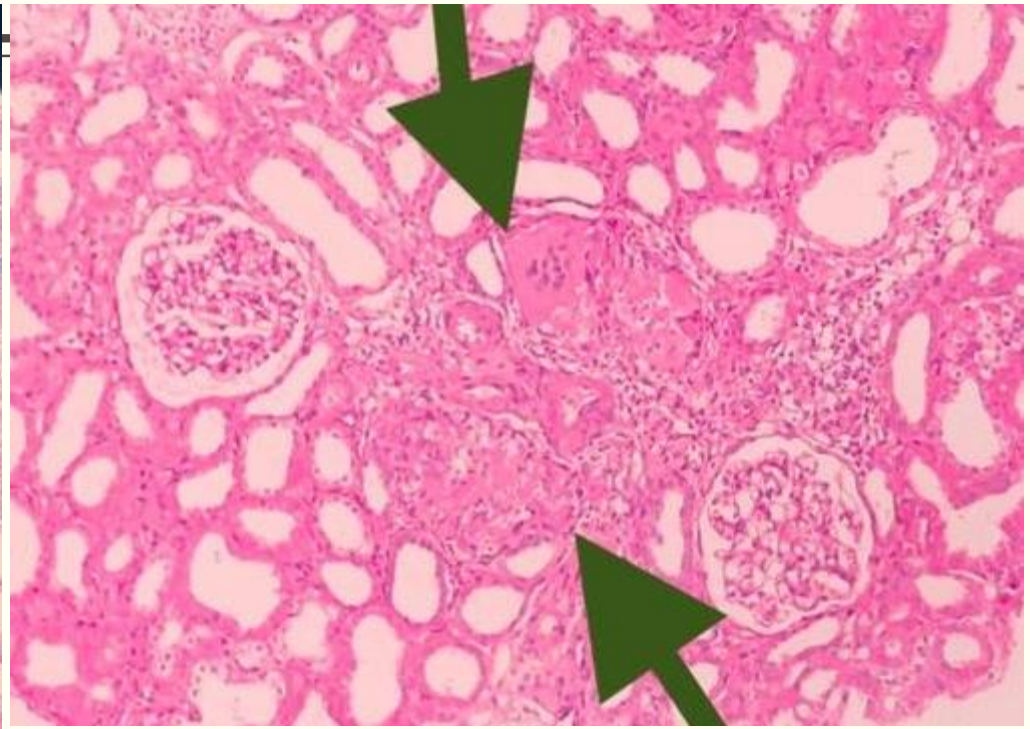
**Milliary nodules in upper lobes, neg for COVID-19**

**US: LK= 116 mm , RK= 112 mm, no stone or hydronephrosis, with spleen diameter=157mm**

# Kidney Biopsy -99

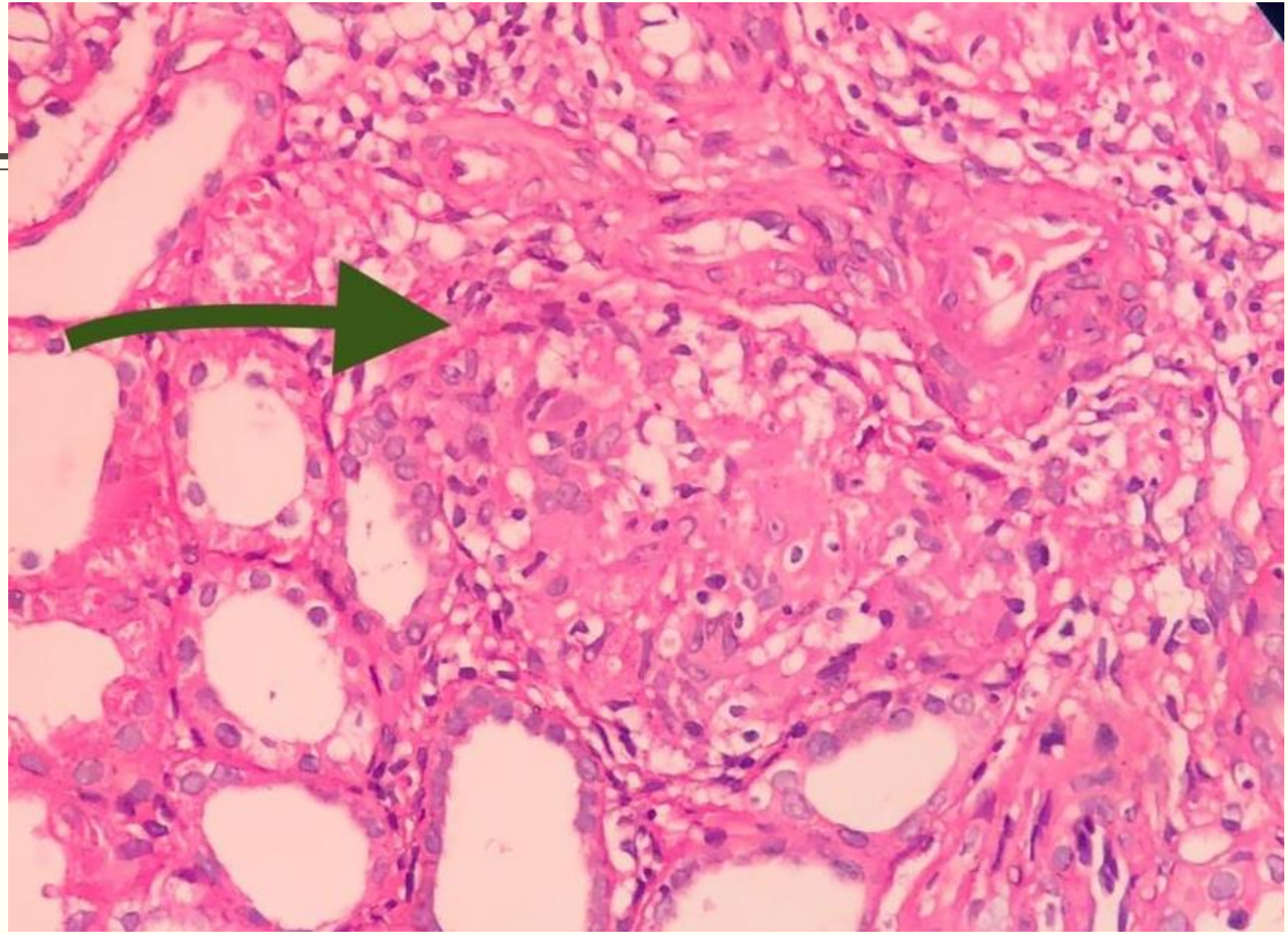


**Granuloma, Masson staining**



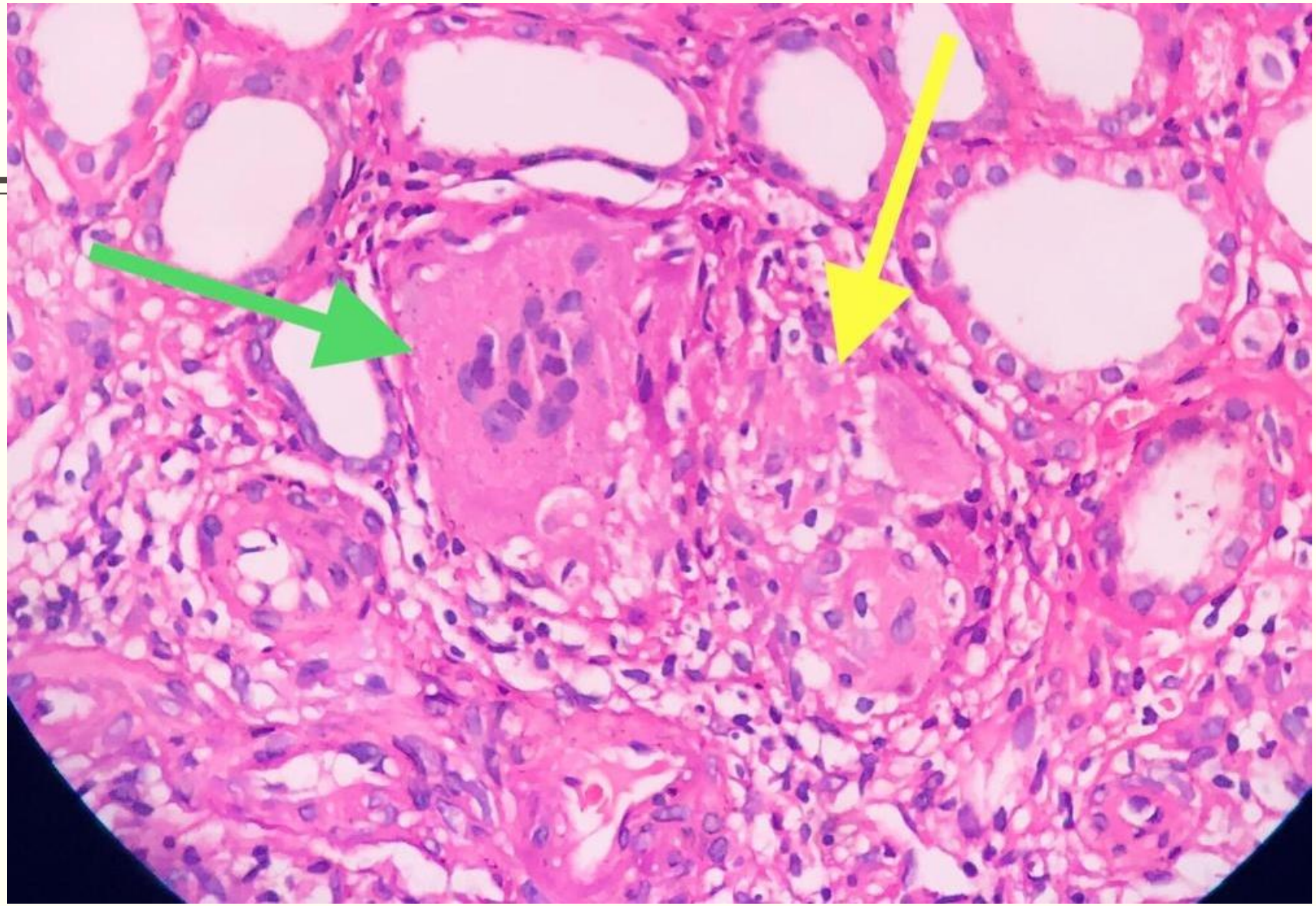
**Granuloma, H&E staining x100**

# Kidney Biopsy



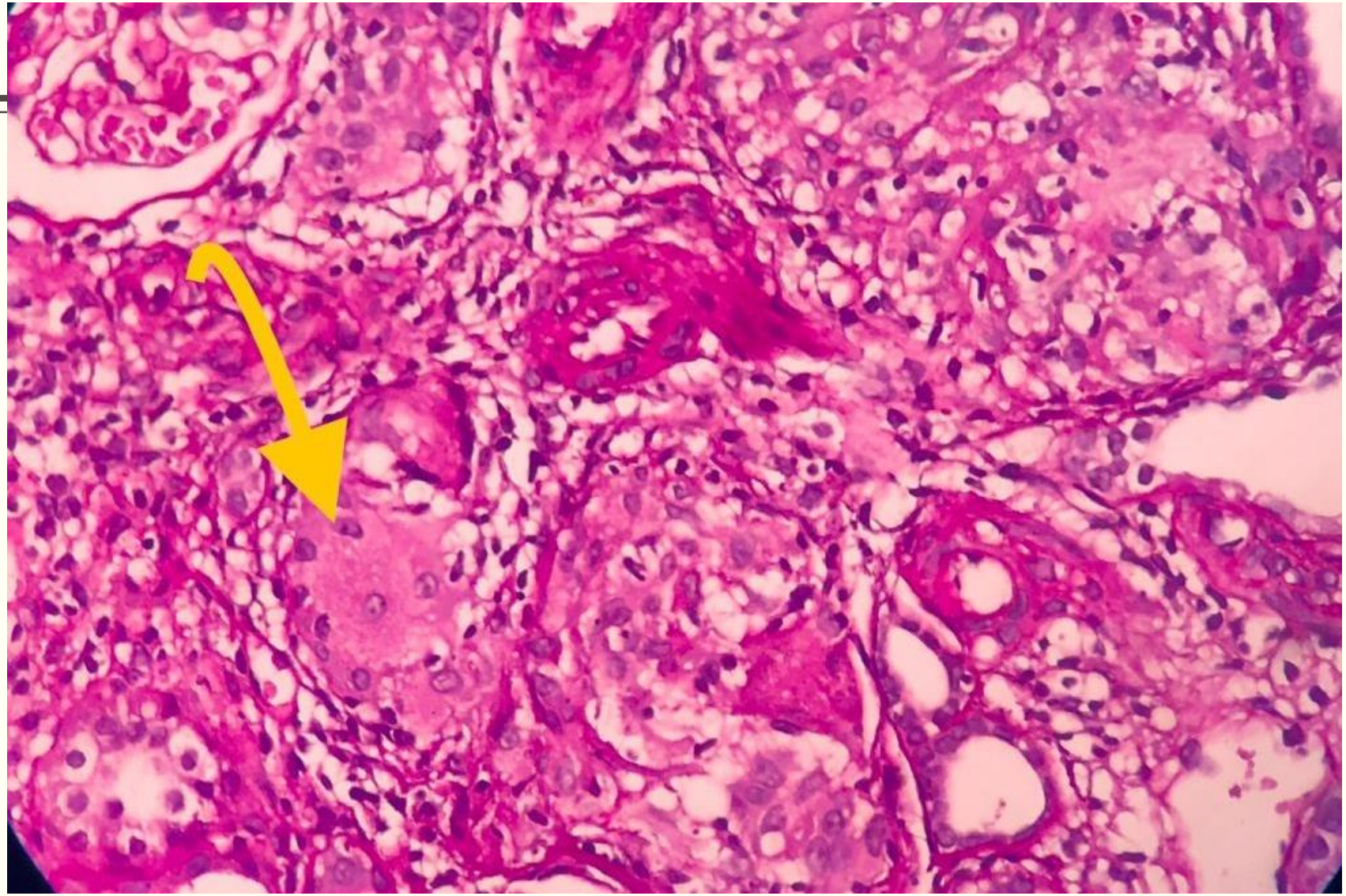
**Granuloma,**
H&E staining x400

# Kidney Biopsy



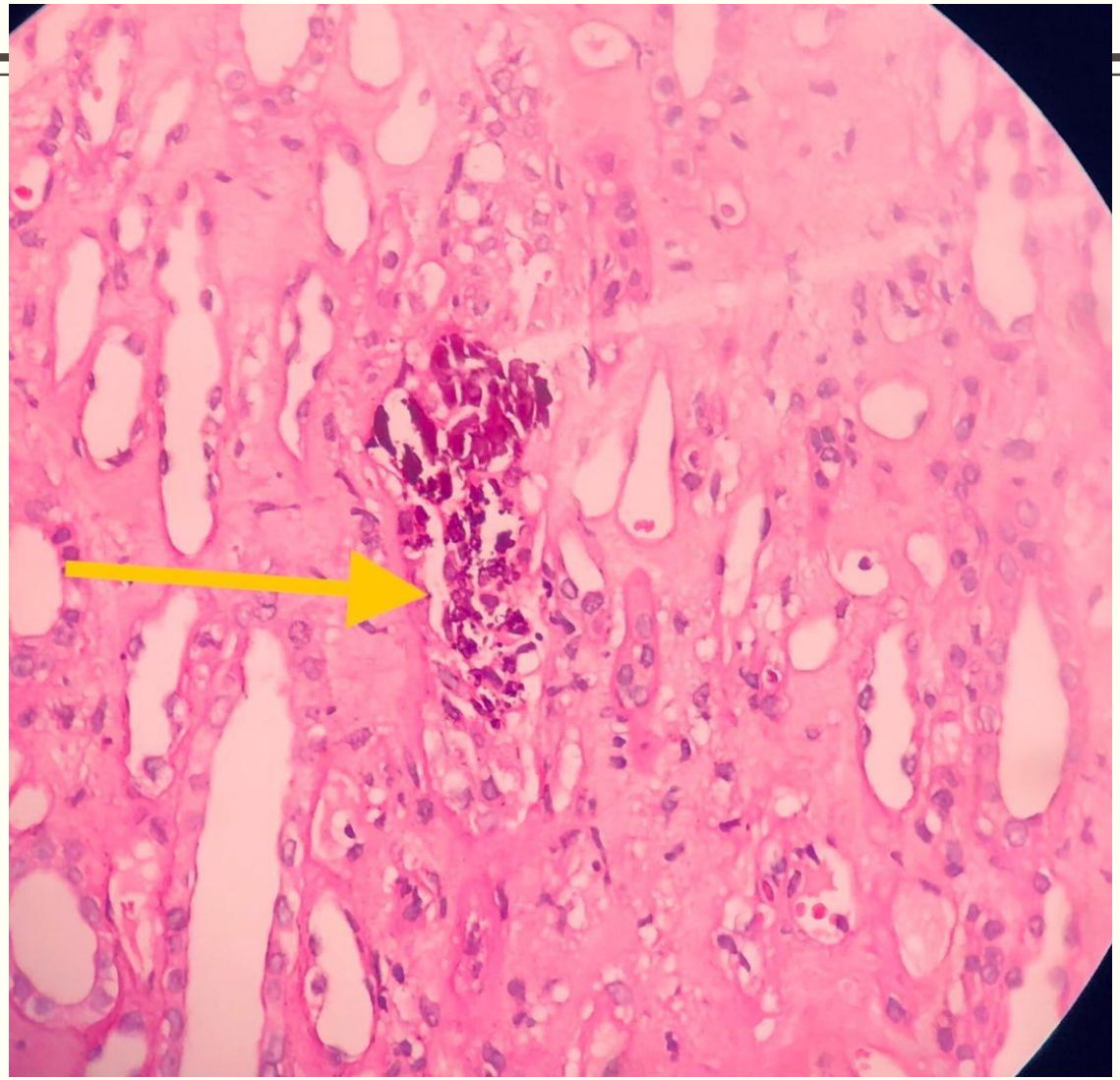
**Multinucleated giant cell (green arrow), Granuloma (yellow arrow)**

# Kidney Biopsy



**Multinucleated giant cell, PAS staining**

# Kidney Biopsy



**Calcium deposition in interstitium**

# Patient diagnosis

- **Radiologic (MDCT):** milliary nodules in upper lobe with respect to bilt hilar LAP in previous CT, probably **sarcoidosis**
- **Kidney biopsy:** acute **TIN**, **granulomatous** type, foci of tubular calcification suggestive of **nephrocalcinosis**
- **Patient discharged and received oral prednisolone 60 mg and Creatinine decreased to 1.32, Ca=9.7 mg/dl.**

# RENAL DISEASE IN SARCOIDOSIS

- **Nephrolithiasis and nephrocalcinosis, and acute interstitial nephritis** with or without granuloma formation.
- Hypercalciuria and hypercalcemia are responsible for renal disease.
- Glomerular disease, obstructive uropathy, and end-stage kidney disease (ESKD) are uncommon
- A survey of **all renal biopsies** over a **six-year period** at **three general hospitals** found clinically significant sarcoid granulomatous interstitial nephritis in **only four cases**
- Hypercalciuria in approximately 40 percent and hypercalcemia in 2 to 20 percent of sarcoidosis.

# Renal disease in sarcoidosis..

## Pathogenesis:

- increased production of calcitriol (1,25 dihydroxyvitamin D,) by activated mononuclear cells (particularly macrophages) in granulomas, the lung, and lymph nodes.

## Clinical manifestations:

- Nephrolithiasis: 2-3.7% of first manifestation of sarcoidosis,
- Nephrocalcinosis± hypercalcemia,
- Polyuria (central or nephrogenic)
- Decreased GFR through preglomerular arteriolar vasoconstriction

# Renal Sarcoidosis

## *Clinical, Laboratory, and Histologic Presentation and Outcome in 47 Patients*

*Matthieu Mahévas, MD, Francois Xavier Lescure, MD, Jean-Jacques Boffa, MD, PhD, Victoire Delastour, MD, Xavier Belenfant, MD, Catherine Chapelon, MD, Carole Cordonnier, MD, Raifat Makdassi, MD, Jean-Charles Piette, MD, Jean-Marc Naccache, MD, Jacques Cadranel, MD, PhD, Pierre Duhaut, MD, PhD, Gabriel Choukroun, MD, PhD, Jean Pierre Ducroix, MD, and Dominique Valeyre, MD*

**Abstract:** We conducted the current study to investigate the clinical, laboratory, and histologic features at presentation and the outcome of renal sarcoidosis (RS). Exhaustive retrospective data were collected by the French Sarcoidosis Group. Forty-seven adult patients were assessed (30 male/17 female, M/F ratio: 1.76). Median estimated glomerular filtration rate (eGFR) was 20.5 mL/min per 1.73 $m^2$ (range, 4–93 mL/min per 1.73 $m^2$). Moderate proteinuria was found in 31 (66%) patients (median, 0.7 g/24 h; range, 0–2.7 g/24 h), microscopic hematuria in 11 (21.7%) patients, aseptic leukocyturia in 13 (28.7%) patients. Fifteen of 47 (32%) patients had hypercalcemia (>2.75 mmol/L). Eleven of the 22 (50%) patients diagnosed between June and September had hypercalcemia compared with only 4 of the 25 (16%) cases diagnosed during the other months ($p < 0.001$). Thirty-seven patients presented with noncaseating granulomatous interstitial nephritis (GIN), and 10 with

We conclude that hypercalcemia and fever at presentation are often associated with RS; RS is most often and permanently responsive to corticosteroid treatment, but some degree of persistent renal failure is highly frequent and its degree of severity in the long run is well predicted from both histologic fibrotic renal score and response obtained at 1 month.

(*Medicine* 2009;88: 98–106)

**Abbreviations:** 25OHD3 = 25OH-vitamin D3, CI = confidence interval, CKD = chronic kidney disease score, CT = computed tomography, eGFR = estimated glomerular filtration ratio, GIN = noncaseating granulomatous interstitial nephritis, MP = intravenous pulse methylprednisolone, OR = odds ratio, PTH = parathormone, RS = renal sarcoidosis

*Medicine* • Volume 88, Number 2, March 2009

# Renal disease in sarcoidosis..

In one study among 47 patients with sarcoidosis interstitial nephritis, 44 presented with an elevated creatinine at diagnosis.

Most patients with renal involvement have clear evidence of diffuse active sarcoidosis

**Urinalysis:** either normal or only sterile pyuria or mild proteinuria

**Diagnosis: elevated** serum **creatinine** and **bland urine sediment** and a known diagnosis or characteristic presentation of **extrarenal sarcoidosis. Strongly** suggested by **renal biopsy**.

# Renal disease in sarcoidosis..

## Diagnosis:

**There is no single diagnostic test for sarcoidosis**

- **Granulomatous interstitial nephritis**, exclusion of other etiologies and **extrarenal manifestations** of **sarcoidosis.**
- Occasionally, patients with renal sarcoidosis have no extrarenal manifestations of sarcoidosis upon presentation.

# Renal disease in sarcoidosis.. Diagnosis..

- **All patients with granulomatous interstitial nephritis** on biopsy should have a chest radiograph and pulmonary function tests and,
- If nondiagnostic, a high-resolution chest computed tomography (HRCT) scan to evaluate for pulmonary sarcoidosis
- Serum calcium, 24-hour urinary calcium concentration, and a serum angiotensin-converting enzyme (ACE) concentration support the diagnosis of sarcoidosis.

# Renal disease in sarcoidosis.. Differential Diagnosis

## Granulomatosus interstitial nephritis:

- Drug-induced interstitial nephritis,
- Tuberculosis, other mycobacterium infections,
- GPA,
- Brucellosis,
- Histoplasmosis,
- Tubulointerstitial nephritis with uveitis (TINU) syndrome,
- Crohn disease (rarely)

# Treatment of sarcoidosis

**Glucocorticoids** (decrease inflammatory activity and calcitriol synthesis),

- Oral prednisone 1 mg/kg/day for 6 to 12 weeks, followed by a slow taper thereafter to a maintenance dose of 10 to 20 mg for an additional six to nine months
- Some patients need low doses indefinitely
- Chloroquine, or Hydroxychloroquine, and
- Ketoconazole

Thanks for your patience